The price to pay

Consequences of paediatric critical illness and the role of parenteral nutrition.

Esther van Puffelen

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The Price to Pay

Consequences of paediatric critical illness
and the role of parenteral nutrition

De prijs die betaald moet worden

Consequenties van kritieke ziekte bij kinderen
en de rol van parenterale voeding

Proefschrift

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Voor mijn ouders

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Chapter 1

General Introduction

Optimal Nutrition in the Paediatric Intensive Care Unit

Partly based on:
Joosten KFM
van Puffelen E
Verbruggen SCAT
Optimal Nutrition in the Paediatric ICU

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INTRODUCTION

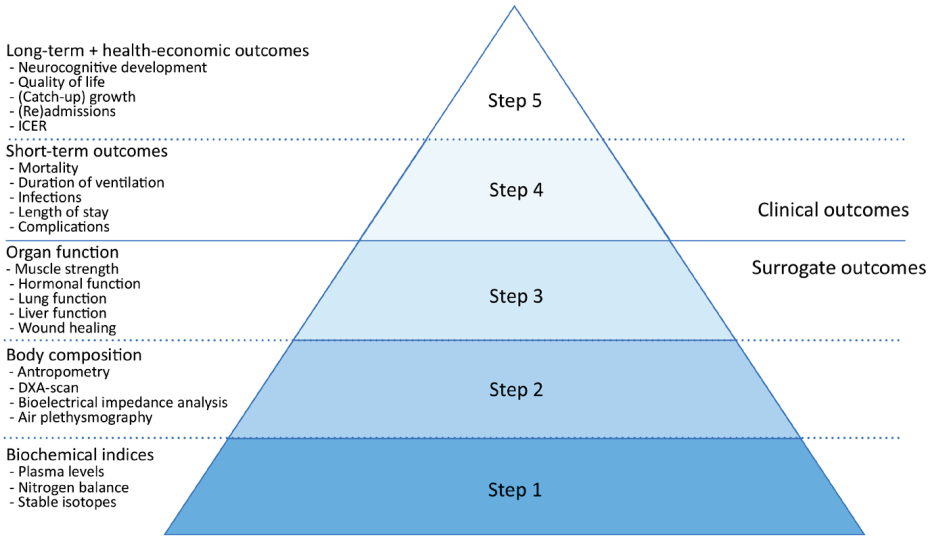
Nutrition is essential for adequate growth and development in all children. In times of critical illness, the acute metabolic stress response temporarily inhibits these processes in favour of the teleological impulse to survive. Alongside this, optimal nutrition deserves a prominent position in intensive care therapy because critically ill children are at high risk of developing nutritional deficiencies due to limited body reserves of fat and protein while energy expenditure is higher. In several studies, nutritional deficits in critically ill children were associated with increased catabolism,[1-3] nutritional status deterioration,[4-7] and worse clinical outcomes.[8,9] Although these studies were not designed to provide causal relations between nutritional deficiencies and clinical outcomes, these associations form the basis of presumed benefit of aggressive feeding strategies to achieve optimal nutrition in critically ill children.

DEFINING OPTIMAL NUTRITION

When applying a nutritional intervention, one should take into account the phases of illness, since an intervention could be beneficial during one phase, yet have detrimental effects when applied in another phase. The first phase of critical illness is the acute phase, in which children admitted to the paediatric intensive care unit (PICU) require (increasing) vital organ support. After the acute phase comes the stable phase, characterised by stabilisation or weaning from vital organ support, followed by the recovery phase, in which the child is no longer in need of vital organ support. During the evolution of these phases of illness, metabolic, immunologic and endocrine alterations occur, which require different nutritional needs.[10]

To define optimal nutrition, a distinction can be made between surrogate and clear clinical outcome parameters. A stepwise approach can be used to describe these surrogate (step 1, 2, 3) and clinical (step 4 and 5) outcome parameters (Figure 1). A summary of these outcome parameters is given in Table 1.

Figure 1: Stepwise approach defining optimal nutrition



ICER = incremental cost-effectiveness ratio.

STEP 1: BIOCHEMICAL INDICES

Biochemical changes predominantly found in the acute phase of critical illness are characterisations of a hypercatabolic state, while in the stable and recovery phase they might reflect the child's nutritional status. Biochemical indices that can be obtained at the bedside include plasma concentrations of glucose, albumin, triglycerides, fatty acids, trace elements, and vitamins. Other indices such as amino acid levels, nitrogen balance, and stable isotope tracer investigations are not easily obtained.

Amino acid concentrations

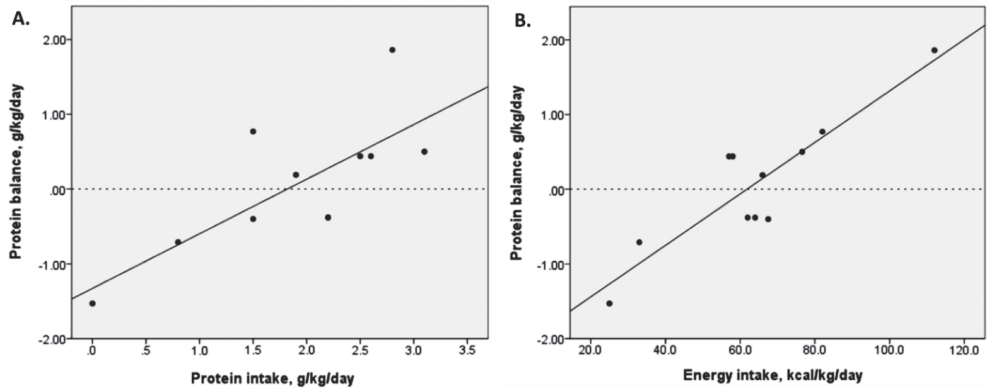
A few recent studies analysed the amino acid profiles of critically ill children after an intervention. A sub-analysis (n=100) of a large randomised controlled trial (RCT) in critically ill children post-cardiac surgery showed amino acid profiles at different time points under conditions of two different glycemic control strategies.[11] Both increased as well as decreased amino acid profiles were observed at baseline and time profiles also differed considerably. Higher total amino acid concentrations were found in neonates and in non-survivors. Whether these differences in specific amino acids reflected nutritional status or catabolism remains unclear. Furthermore, several studies on critically ill infants, with a limited number of patients, have shown that amino acid profiles can be affected by modulating both enteral and parenteral nutrition.[2,12-14] Whether plasma amino acid levels can be used to estimate protein catabolism and to guide nutritional interventions is currently under debate. Recent findings show that low blood amino acid levels are the result of increased availability of glucagon,

which stimulates hepatic amino acid breakdown and ureagenesis, and is even intensified by exogenous amino acid administration.[15-17]

Nitrogen balances

Commonly used methods to calculate protein turnover are nitrogen balance and stable isotope tracer infusion. Although nitrogen balance is predominantly used, this method requires an adaptation period which is extremely difficult to establish in critically ill children. In a systematic review of 9 studies, a correlation between energy and protein intake and protein balance in critically ill children on mechanical ventilation was shown. A minimum intake of 1.5 g/kg/day protein and 57 kcal/kg/day energy was associated with a protein anabolic state (Figure 2).[3]

Figure 2: Protein balance associated with the corresponding level of A, protein intake (Spearman r=0.729; p=0.011) and B, energy intake (r=0.721; p=0.012) in critically ill children (adapted with permission from Bechard LJ et al.[3])



Stable isotopes

In contrast with nitrogen balance studies, stable isotope tracer studies only require a steady state for a period of hours instead of days. In stable isotopes studies in critically ill infants and adolescents, high protein intake (3 g/kg protein) compared with 1.5 g/kg protein provided net positive protein balance.[1,2] However, in septic adolescents this beneficial effect was offset by enhanced endogenous glucose production and lipolysis, which raised concerns of an increased insulin resistance.[1]

Glucose homeostasis

One of the measurements that can easily be obtained at the bedside is blood glucose concentration, which is influenced by macronutrient intake and metabolism, and is regulated by hormones. Hyperglycaemia frequently occurs during the acute phase of critical illness and is a complication commonly feared among paediatricians. In a recent RCT with the acronym

"PEPaNIC" (Paediatric Early versus Late Parenteral Nutrition in Critical Illness), in which critically ill children were randomly allocated to early initiation (<24 hours) of supplemental parenteral nutrition (PN) or withholding PN during the first week, the risk of hypoglycaemia was increased in the Late-PN group.[18] Both the correct definition of hypoglycaemia and the long-term consequences of a brief period of low glucose levels without clinical signs remain uncertain.[19-23] In contrast, hyperglycaemia above 145 mg/dL (above 8 mmol/L) has consistently been associated with increased morbidity and mortality.[24,25] A meta-analysis of 4 trials in critically ill children revealed that tight blood glucose control did not decrease mortality, but reduced new infections, at the expense of higher incidence of hypoglycemia.[26]

Lipids

Dyslipidaemia during critical illness is characterised by increased plasma triglycerides, free fatty acids, and very-low-density lipoproteins (VLDL) on the one hand and a decreased cholesterol content of both high- and low-density lipoproteins (HDL, LDL) on the other. A number of factors may decrease the clearance rate of lipids and increase the level of serum triglycerides: malnutrition (lower levels of lipoprotein lipase), the lipolytic effect of drugs (like steroids), lipid-containing drugs (like propofol, amphotericin B), metabolic stress, and organ dysfunction. Upper limits for plasma triglycerides are used to guide optimal lipid provision: for infants a level of >250 mg/dL (>2.9 mmol/L) and for older children >400 mg/dL (>4.6 mmol/L). Providing lipids allows a high energy supply, facilitates the prevention of high glucose infusion rates, and is indispensable for the supply of essential fatty acids. However, the optimal composition remains a topic of discussion. Although immunomodulation with different fatty acid compositions has gained widespread interest, studies in critically ill children are scarce. In critically ill children, enteral nutrition (EN) enriched with eicosapentaenoic acid and γ-linolenic acid effectively modulated plasma phospholipid fatty acid concentrations, theoretically reflecting an anti-inflammatory profile.[27] The use of soybean oil emulsions, which have been the primary choice for years, was associated with compromised immune function and PN associated liver disease. Although a recent systematic review did not find significant evidence that a combined lipid emulsion offers any benefit as compared with a soybean oil emulsion,[28] pure soybean oil emulsions may provide less balanced nutrition than combined lipid emulsions.[29] If a child depends on PN longer than a few days, recently updated European guidelines recommends replacing pure soybean oil emulsions by combined lipid emulsions with or without fish oil.[29] Fish oil based or combined lipid emulsions are capable of changing the fatty acid plasma profile and antioxidant defense system in children.[30]

Overall, there are several studies that have looked at plasma levels of macronutrients during critical illness as well as their changes after a nutritional intervention. In clinical practice, advanced biochemical indices are hard to obtain, which makes them less suitable to guide daily nutritional management. However, biochemical indices are important scientific outcome measures to give more insight into the underlying mechanisms of nutritional interventions. When using these outcomes, one should keep in mind that an improved biochemical outcome does not necessarily translate into better outcomes for the patient.

Therefore, if possible, findings from studies using biochemical outcomes should be related to short- and long-term clinical outcomes.

STEP 2: BODY COMPOSITION

Anthropometry

Changes in nutritional status are traditionally assessed by alterations in body composition, predominantly with the use of anthropometric measurements including weight, height, and head circumference. Alternatively, mid-upper arm circumference can be used to identify undernutrition or to estimate a child's weight.[31,32]

To diagnose undernutrition and overweight in children, Z-scores for weight-for-age, weight-for-length, length-for-age, and body mass index (BMI)-for-age are commonly used. Z-scores can be based on the World Health Organisation child growth standards, or on country or syndrome-specific growth charts. Children with a Z-score <-2 are considered undernourished in most studies. A few studies have reported the relationship between altered body composition, measured with anthropometric variables, and outcomes. In a study of 385 children admitted to a PICU, 45% were undernourished on admission, which was associated with an increased duration of mechanical ventilation (6.3 vs 5.1 days).[33] Several other studies showed an association between undernutrition and multi-organ failure, mortality, prolonged PICU stay, and duration of mechanical ventilation.[34-36] Currently, it is not clear whether overweight or obesity is associated with the impaired outcome on the PICU.[37-41]

There is a scarcity of data addressing the evolution of body composition during admission and at follow-up, and the effect of nutrition hereon. In an observational study of 293 critically ill children, the nutritional status deteriorated from admission to discharge, but recovered within 6 months after discharge.[42] Lower enteral intake was associated with deterioration of the nutritional status.[4-7] In a study of 325 children who stayed at least 4 days at the PICU, 19% were acutely undernourished on admission.[43] In a subgroup of 223 children, the proportion of acutely undernourished children at discharge (26%) was not significantly different from that on admission (22%).[43] In this study, no association was found between the amount of energy intake or route of nutrition and clinical outcomes, but this study was not designed to find these differences.[43] In a recent study, faltering growth – defined as a deceleration of >1 Z-score within 3 months – during the first year after PICU admission was associated with a longer length of PICU stay.[44] However, the role of nutrition during PICU stay was not investigated in this study.

Dual X-ray absorptiometry, bioelectrical impedance analysis, air plethysmography

In the PICU, other methods to measure nutritional status such as dual X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), and air plethysmography are still rarely performed due to the practical and logistic limitations of these measurements. In one study, in which 592 children with burns were studied, DXA was used on admission and discharge. A higher loss of bone mineral density was found in obese children whereas normal weighing

hospital stay and the loss of lean body mass was nearly equal in both groups.[45] Recently, the prognostic value of a phase angle measurement by use of BIA (which is a measure of undernutrition) was investigated in children admitted following congenital heart defect surgery. A lower phase angle on admission to the PICU and at day 2 was associated with a PICU stay longer than 4 days,[46] suggesting that this can possibly be used as a very early outcome measure to predict short-term clinical outcomes.

It can be concluded from the literature that undernutrition on admission to a PICU is associated with impaired outcomes. So far, it is unknown whether short-term changes in body composition predispose for long-term sustained body composition alterations. Furthermore, it is unknown if and how nutritional interventions during PICU stay can alter the course of a nutritional status, as there are no studies investigating a causal relation. If a nutritional status would be modifiable, it is unknown whether preventing deterioration of it actually leads to improved clinical, long-term outcomes. Thus, the value of body composition as a measure of outcome is still unclear.

STEP 3: ORGAN FUNCTION

Optimal nutrition might enhance recovery of organ functions (nerve, muscle, hormonal function, lung, liver, skin).

Muscle strength

The reported incidence of muscle weakness in critically ill children varies from 1.7% to 30%.[47,48] Muscle mass, as measured by the thickness of the femoral quadriceps, decreased up to 13% during PICU stay.[49] Muscle and nerve dysfunction exacerbated by critical illness already begins within hours of PICU admission,[50] and was associated with functional disability in adults,[51,52] and with both a longer need for mechanical ventilation and longer length of PICU stay in children.[53] After the acute phase, handgrip strength can be tested in children aged 4 years and older to investigate muscle function. In observational studies in hospitalized non-critically ill children, there was an independent association between inflammation and handgrip strength.[54] In critically ill mice and adults, PN was not capable of preventing muscle wasting.[16] In fact, early administration of PN increased muscle weakness and reduced autophagic quality control of myofibres.[55] The absence of an effect of PN on muscle wasting might be explained by increased hepatic amino acids breakdown, mediated by higher glucagon availability, which is enhanced by amino acid administration.[16] Currently, it is unknown whether nutrition can affect muscle mass or function in critically ill children.

Hormonal function

One of the hormonal axes affected by critical illness is the thyroid axis, leading to non-thyroidal illness syndrome (NTI), which is characterised by an increased peripheral inactivation of thyroid hormone. The severity of NTI was associated with a prolonged duration of PICU stay

in critically ill children with meningococcal sepsis.[56] In critically ill adults with low or no macronutrient intake, NTI was further aggravated.[57] In a small RCT among critically ill children with severe burns, initiating EN after 48 hours resulted in lower T3 concentrations, compared to when EN was initiated within 24 hours.[58] In a mixed group of critically ill children, a fasting response mimicked by tight glycaemic control resulted in a more pronounced peripheral inactivation of thyroid hormone.[59] This aggravated peripheral inactivation was associated with a higher likelihood of an earlier live discharge from the PICU, suggesting that enhancement of the early catabolic response to critical illness might be beneficial. Regarding the somatotropic axis, tight glycaemic control in critically ill children led to increased blood growth hormone concentrations and decreased bioavailable insulin-like growth factor-1, possibly partly due to increased peripheral growth hormone resistance.[60] In contrast with all other hypothalamus-pituitary-peripheral axes, the hypothalamus-pituitary-adrenal axis shows a pattern of typically high cortisol levels, with low levels of adrenocorticotropic hormone. Although nutrition can influence the cortisol concentration in healthy individuals, in critically ill adults, early administration of PN did not result in elevated cortisol levels, compared to when PN was postponed beyond the first week of admission to the intensive care unit.[61]

The studies addressing tight glycaemic control in critically ill children showed that a metabolic/nutritional intervention is capable of altering hormone levels. To what extend the hormonal axes of critically ill children can be affected by nutrient intake has not been explored yet.

Lung function

In regard to lung function in mechanically ventilated children, weaning from mechanical ventilation is dependent on several pathophysiological conditions, such as neuromuscular incompetence, diaphragmatic muscle weakness, and nutritional disorder. Currently, no studies exist that have shown nutritional status or nutritional strategies to affect either lung function or weaning parameters.

Liver function

Abnormal blood levels of liver enzymes often indicate liver dysfunction and are routinely used in clinical practice. The PEPaNIC RCT showed that withholding PN during the first week in PICU (Late-PN) resulted in lower peak plasma concentrations of gamma-glutamyl transpeptidase (γ-GT) and alkaline phosphatase (ALP), and in higher plasma total bilirubin concentration, as compared with Early-PN.[18] Alkaline aminotransferase (ALAT) and aspartate aminotransferase (ASAT) were unaffected by PN.[18] However, when the plasma concentrations of γ-GT, ALP, ALAT, and ASAT were analysed per day, there we no differences between the randomised groups.[62] Daily plasma bilirubin concentrations were elevated by Late-PN but were comparable to those of the Early-PN group when PN was started after 1 week.[62] Further evaluation of these findings revealed that, during the first week, the prevalence of cholestasis (3.8%-4.9%) and hepatitis (0.8%-2.2%) were low, and unaffected by PN.[62] A mild elevation of

plasma bilirubin at day 1, between 0.20 mg/dL and 0.76 mg/dL, was associated with a lower risk of mortality.[62]

Wound healing

In case of burn injury, skin healing is an important treatment outcome. Recovery is characterised by catabolic and hypermetabolic responses that may persist for up to 2 years. Only 1 study with a small group (18 children, 20-40% total body surface burned) showed that an increase of dietary protein intake from 1.1 to 2.9 g/kg/day might enhance skin healing.[63] So far, however, no RCTs in children with burns have studied the influence of nutritional strategies on skin healing.

It can be concluded that studies which relate nutrition to organ function are scarce. These outcome parameters could be of interest, as some organ dysfunctions persist in the long-term, which could impair the daily functioning and quality of life of PICU-survivors.

STEP 4: SHORT-TERM CLINICAL OUTCOMES

In the past decades, the advancement of new techniques has led to a decline in mortality rates of PICU patients to <5% in developed countries.[18,64] Subsequently, measures of morbidity have become more important. Other short-term clinical outcome measures are length of stay (PICU or hospital), duration of mechanical ventilation, incidence of new infections and other complications. Numerous studies showed a clear association between malnutrition and these outcomes. Some recent studies suggested that early nutritional support might influence the short-term outcomes. In a retrospective study of 306 children between 8 and 18 years of age with traumatic brain injury, a shorter time to initiation of nutritional support was associated with a decreased length of stay, and a shorter time to reach full caloric intake was associated with improved neurological status at discharge.[65] A multicentre retrospective study, performed in 5105 critically ill children with a PICU length of stay of ≥4 days, showed that children who received at least 25% of targeted energy intake enterally over the first 48 hours of admission, were less likely to die than those who did not.[66] Recently, in two multicentre prospective cohort studies in children older than 1 month who required mechanical ventilation longer than 48 hours, it was shown that higher enteral intake (67% of targeted intake) and delivery of more than 60% of prescribed protein intake were associated with lower 60-day mortality.[8,9] It should be noted that all abovementioned studies were observational, which includes a risk of confounding, as both nutritional intake and clinical outcome can be affected by the severity of illness, medication, age, and many other variables. One small RCT has been performed in children with severe burns, investigating initiation of EN within 24 hours versus after 48 hours, in which no effect on clinical outcomes was found.[58] However, this study might have been underpowered. Overall, it is widely accepted, but based on predominantly observational studies, that early initiation of EN and higher enteral intake is preferred.

If caloric targets cannot be reached by EN, supplemental PN is routinely used in the PICU.[67] In a previous observational study, the use of PN was associated with higher mortality.[8] Recent systematic reviews showed that there is a scarcity of RCTs investigating PN in critically ill children using clinical outcomes.[68,69] Currently, 1 large RCT has been done to investigate the effects of PN. In 2016, the short-term clinical results from the multicentre, international RCT "PEPaNIC" were published.[18] In this study, 1440 critically ill children, with an expected PICU stay longer than 24 hours, and expected insufficient EN longer than 24 hours were randomized into "Early-PN" (initiation of PN within 24 hours) or "Late-PN" (withholding PN during the first week) if the exclusion criteria were not met. This study was executed in the PICUs of Leuven (Belgium), Rotterdam (The Netherlands), and Edmonton (Canada). The children were aged from term newborns to 17 years. Children in the Early-PN group received PN to supplement EN until the amount of calories delivered enterally was above 80% of target. In the Late-PN group, a dextrose 5%/saline mixture was administered intravenously until EN was above 80% of target to match the amount of fluid administered to children in the Early-PN group. At day 8, PN was also started in the Late-PN group if EN was still insufficient. Initiation and incline of EN were similar in the treatment groups and all children received intravenous vitamins, minerals, and trace elements if EN was under 80% of target.

In this study,[18] Late-PN was clinically superior to Early-PN on relevant outcome measures: among others, it reduced the incidence of new infections and shortened length of PICU and hospital stay. There was no significant difference in mortality. However, the incidence of hypoglycaemia (<40 mg/dL [<2.2 mmol/L]) was higher in the Late-PN group. Furthermore, a post hoc secondary analysis from this study showed that higher doses of amino acids, but not lipids or glucose, were associated with an increased risk of acquiring new infections, a longer duration of PICU dependency, and a longed need for mechanical ventilatory support.[70]

Aside from the position this trial took in the new guidelines, another major contribution was that it provided firm support for the role of nutrition as therapeutic intervention for critically ill children. Interestingly, children with the highest risk of malnutrition benefitted the most from Late-PN regarding the primary outcomes.[18] Furthermore, term neonates had a larger reduction in length of PICU stay with Late-PN than older children.[18] Since the clinical short-term outcomes were not analysed in detail in these subgroups, many questions remained unanswered. Hence, concerns were raised by nutritional experts on the efficacy and safety of withholding PN for a week in undernourished children and neonates.[71-75] Furthermore, concerns were raised on possible weight deterioration due to reduced nutritional intake.[71] Thus, this RCT provided important answers and showed that nutrition can impact clinical outcome, yet also raised new questions, which need to be addressed.

From the current literature, it can be concluded that early (within 48 hours) and higher (67% of goal) enteral intake is associated with better short-term outcomes, although evidence for causality is lacking. Adequate EN can be achieved by the choice of an appropriate route of enteral feeding, by the timing of the start of EN, by administering protein-energy enriched

formula and by overcoming the common barriers to start or continue EN.[76,77] Based on 1 RCT it can be concluded that withholding PN during the first week results in improved short-term outcomes. There is a need for more RCTs investigating the effect of nutritional intervention on short-term outcome parameters.

STEP 5: LONG-TERM AND SOCIETAL HEALTH-RELATED ECONOMIC OUTCOMES

Physical outcomes

Children who are discharged from the PICU and hospital often suffer for years from sustained morbidity.[78,79] Children with oesophageal atresia showed impaired growth up to the age of 8 years, which was normalised at age 12 years.[80] On the contrary, children with congenital diaphragmatic hernia showed impaired growth up to age 12 years.[81] Furthermore, post-PICU patients are at risk of developing chronic kidney disease. Among children who developed acute kidney injury during PICU stay, 10% were diagnosed with chronic kidney disease 1 to 3 years after critical illness.[82] Long-term prevalence of persistent critical illness-induced muscle weakness was described up to 30% in children who developed muscle weakness during PICU stay.[83]

Recently, a 6-month and 3-year follow-up of post-PICU patients revealed that mortality increased from 4% at discharge from PICU to 8% at 6 months and 10% at 3 years.[79] New morbidity, defined as a change in Functional Status Scale score of ≥3, also increased during follow-up from 5% at discharge from PICU to 7% at 6 months and 10% at 3 years.[79] These findings point out that the burden of critical illness is not limited to the PICU or hospital period, and stresses the importance of long-term follow-up.

Neuropsychological outcomes

Nutrition is one of many factors that can affect brain structure and function, cognition, and academic performance.[84,85] The brain is particularly vulnerable to an inadequate diet in the phase of rapid growth in the last trimester of gestation and the first 2 years after birth.[86] A recent systematic review showed that PICU survivors have significantly lower scores in at least 1 cognitive domain compared to healthy controls.[87] This cognitive impairment was associated with low socioeconomic status and signs of more severe illness, such as high oxygen requirements, need for mechanical ventilation, sedation, and pain medications.[87] A younger age at critical illness and/or older age at follow-up were associated with cognitive impairment,[87] which could be explained by a phenomenon called 'growing into deficit': brain damage evoked earlier in childhood could have a cumulative effect on neurodevelopment, since more cognitive skills are demanded with increasing age, making neurocognitive deficits more pronounced.

Furthermore, a literature review showed that paediatric critical illness decreased health-related quality of life.[88] These findings in the general PICU population were also present in specific subgroups of post-PICU patients. Children who were treated with extracorporeal membrane oxygenation showed a lower health-related quality of life, behavioural problems,

and neurocognitive impairments with a normal intelligence quotient (IQ) years after critical illness.[89-91] Children who survived meningococcal septic shock syndrome, cardiac arrest, cardiac surgery or heart transplantation also had neuropsychological problems.[92-95] The long-term 'legacy' of critical illness was traditionally presumed to be unmodifiable during the course of critical care. This is in contrast to a large long-term follow-up performed in children who were randomised to standard or tight glycaemic control during PICU admission 4 years earlier. The post-PICU patients had a full-scale IQ reduction of 9 points and scored worse on executive functioning, memory, behaviour, and neurological condition compared with siblings and age-matched unrelated healthy controls.[20] More interestingly, tight glycaemic control in these patients improved motor coordination and cognitive flexibility. Tight glycaemic control mimicked a fasting response due to the low circulating levels of glucose, as was shown by the suppressed somatotropic and thyrotrophic axes.[59,60] This mimicked fasting response explained part of the benefit of tight glycaemic control. Hence, interfering with nutrition and metabolism during critical illness has the potential to affect long-term outcomes.

Health-economic outcomes

Along with the long-term consequences of critical illness for children and their families, there is also a societal burden. This burden includes the costs of treatments during PICU admission as well as the lifetime – direct and indirect – health-related costs. There are hardly any studies about the health-economical aspects of nutritional support in critically ill children. Costs of nutrition itself are a small fraction of total PICU costs. The most important attribution to total PICU costs is the length of stay, which is highly related to infectious complications.[96] Reducing PN, an independent risk factor for acquisition of new infections, could inherently substantially cut PICU costs.[97]

To show that nutritional and metabolic interventions can indeed affect both clinical and economic consequences, studies on tight glycaemic control can, again, be used as an example. In a large multicentre study, tight glycaemic control led to an average reduction in 12-month costs of approximately £10,000 for the non-cardiac surgery subgroup.[98] These potential cost savings from a tight glycaemic control policy are important in understanding the possible impact of optimal therapy on financial resources.

Overall, PICU survivors are confronted with long-term significant physical and neuropsychological morbidity, which seems to increase over time. Whether this long-term 'legacy' can be influenced by nutritional interventions is being investigated after the PEPaNIC trial. As presently, more critically ill children survive post-PICU, optimal long-term outcomes are the ultimate goal. Furthermore, as the costs of nutritional support are relatively low, with potentially significant clinical effects, nutritional interventions are likely to be cost-effective. Thus, future nutritional studies should preferably include a long-term follow-up and cost-effectiveness assessment.

CURRENT NUTRITIONAL PRACTICES IN PICUS

Most recommendations on nutritional management in current international guidelines are based on expert opinion, observational studies, or studies with surrogate endpoints.[74,99] This lack of evidence is also reflected in the variety of nutritional management in practice. Recent surveys across the world have investigated the current nutritional practices in PICUs. All of them concluded that nutritional practices varied widely between PICUs.[67,100-102] Presence of a nutritional protocol ranged from 31% to 52%.[67,100-102] Energy requirements were estimated using a variety of methods, particularly the Schofield equation, World Health Organization recommendations, dietary reference index, and based on total fluid requirements.[67,100] EN was intended to be started early (within 24 to 48 hours) in 30% to 60% of the PICUs, preferably via the gastric route (in more than 80% of the PICUs).[67,100,101] In all surveys, the most reported reasons for stopping EN were suspected gastrointestinal intolerance (based on gastric residual volumes, abdominal symptoms/distension, vomiting), hemodynamic instability, suspected necrotising enterocolitis, and after cardiac arrest.[67,100-102] When EN was insufficient, in 13% to 42% of the PICUs, PN would be started within 24 hours;[67,100,101] in approximately 55% of the PICUs, PN would be started within 48 hours.[67,101]

Table 1: Summary of surrogate and clinical outcome parameters

Parameter	Variables and major outcomes	Remarks
Biochemical indices	Plasma amino acid profiles: differ according to disease phase, age and survival status. Can be affected by (par)enteral intake and insulin.	Difficult to achieve in routine clinical care.
	Nitrogen balance and stable isotope studies: higher protein intake increases net protein balance.	Require a steady state, difficult to achieve in routine clinical care.
Body composition	Z-scores of weight and BMI: undernutrition is associated with longer duration of mechanical ventilation, multi-organ failure, prolonged PICU stay, and mortality.	Weight and height are difficult to measure and estimates are used regularly.
	Lower enteral intake is associated with nutritional status deterioration. DXA: a higher loss of bone mineral density was found in obese children with burns. Lower phase angle is associated with prolonged PICU stay.	Effect of PN on the course of nutritional status is unknown. Difficult to achieve in PICU setting.
Organ function	Handgrip strength related to inflammation and undernutrition on admission.	Can be tested after critical illness, age ≥4 years.
	Lower T3 if EN was initiated >48 hours compared to <24 hours in children with burns.	One RCT in children with burns.
	Withholding PN during the first week elevated plasma bilirubin concentration. Mild elevation of plasma bilirubin is associated with lower mortality.	One large RCT.
Short-term outcomes	Mortality: relation with the adequacy of EN and amount of protein. Length of hospital stay and neurological status at discharge after traumatic brain injury: associated with earlier nutritional support.	Observational studies, no evidence for causality.

Table 1 continued

Parameter	Variables and major outcomes	Remarks
Short-term outcomes	In children with burns: initiation of EN <24 vs >48 hours: no difference in clinical outcome.	One small RCT.
	Length of stay, new infections, duration of ventilation: decreased by withholding PN during the first week.	One large RCT.
Long-term outcomes	Improved neurocognitive outcome, primarily motor coordination and cognitive flexibility 4 years after tight glycaemic control in PICU.	Only RCTs on tight glycaemic control; no studies done comparing nutritional strategies.
	Health-economics: reduction in 12-month costs by tight glycaemic control in the non-cardiac subgroup.	No cost-effectiveness studies on nutrition. Difficult to calculate total financial impact.

BMI = body mass index; DXA = dual X-ray absorptiometry; EN = enteral nutrition; PICU = paediatric intensive care unit; PN = parenteral nutrition; RCT = randomised controlled trial.

CONCLUSION

Most nutritional studies in critically ill children were not designed to prove causal relationships between nutritional interventions and clinical outcomes or used surrogate measures of outcome, such as biochemical changes. Subsequently, current international guidelines on nutritional intake are predominantly based on small trials with surrogate outcome parameters.

Understanding the characteristics of the different phases of the acute stress response is essential in defining an optimal strategy concerning enteral and parenteral nutritional support. Recent research has shown that an optimal nutritional strategy depends on the phase of illness, and is influenced by the choice of an appropriate route of feeding, by the timing of (par)enteral nutrition, and by overcoming the common barriers to start EN, which is the preferred route of feeding in the early phase of the disease.

Prospective randomised studies are needed with nutritional and/or metabolic interventions to establish an optimal feeding strategy for critically ill children. These studies should be adequately powered, with clinical short-term outcomes, and preferably include a long-term follow-up and cost-effectiveness assessment.

OUTLINE OF THIS THESIS

The aim of this thesis was to provide more insight into optimal nutrition for critically ill children, and into potential nutritional opportunities to reduce healthcare costs in the PICU. In this thesis, both the clinical consequences and the health-economic consequences of paediatric critical illness are addressed, focusing on the role of PN.

The main hypotheses that we tested were as follows:
Withholding PN during the first week in critically ill children…

- is effective and safe in neonates and undernourished children;
- does not negatively affect nutritional status;
- is effective and safe in the long-term;
- is a cost-saving strategy comprising more than merely omitting the costs of PN itself.

The large multicentre PEPaNIC RCT has shown that Late-PN was clinically superior to Early-PN in critically ill children. Due to the results of the PEPaNIC RCT, Early-PN was de-implemented locally. However, it was unknown to what extent delaying PN was adopted worldwide. This thesis starts with the results from our online survey to investigate the de-implementation of early initiation of PN in PICUs worldwide, and to identify factors that facilitated or hampered de-implementation **(Chapter 2)**. In this thesis, short-term outcomes of Late-PN versus Early-PN in critically ill neonates **(Chapter 3)** and critically ill undernourished children **(Chapter 4)** are explored. In order to further investigate the safety of tolerating a low macronutrient intake, the change in weight during PICU admission in both treatment groups is described **(Chapter 5)**. In recent years, there has been more focus on the long-term consequences of paediatric critical illness. In this thesis, the long-term neuropsychological development of PICU survivors of the PEPaNIC trial are described **(Chapter 6)**. Besides the clinical consequences of critical illness, there is also an economic burden. In **Chapter 7**, the cost-effectiveness of Late-PN versus Early-PN is addressed, and the impact of preventing new infections by Late-PN on the total direct healthcare costs is explored. Finally, this thesis concludes with a discussion of the results and aims for future research **(Chapter 8)**. An English and Dutch summary of the major findings that are presented in this thesis can be found in **Chapter 9**.

Chapter 2

Worldwide Survey of De-implementation of Initiating Parenteral Nutrition Early in Paediatric Intensive Care Units

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ABSTRACT

Background

Initiating parenteral nutrition (PN) within 24 hours in critically ill children is inferior to withholding PN during the first week, as was found in the PEPaNIC study. The aims of this study were to investigate de-implementation of early initiation of PN at PICUs worldwide, and to identify factors influencing de-implementation.

Methods

A cross-sectional online survey was conducted (May-October 2017), consisting of 41 questions addressing current PN practices, the degree of de-implementation, and factors affecting de-implementation.

Results

We analysed 81 responses from 39 countries. Of these 81 respondents, 53 (65%) were aware of the findings of the PEPaNIC study, and 43 (53%) have read the article. In these 43 PICUs, PN was completely withheld during the first week in 10 PICUs, of which 5 already withheld PN (12%), and 5 de-implemented early initiation of PN (12%). Partial de-implementation was reported by 17 (40%) and no de-implementation by 16 (37%). Higher de-implementation rates were observed when the interpreted level of evidence and grade of recommendation of PEPaNIC was high. Predominant reasons for retaining early initiation of PN were concerns on withholding amino acids, the safety in undernourished children and neonates, and the long-term consequences. Furthermore, the respondents were waiting for updated guidelines.

Conclusions

One year after the publication of the PEPaNIC trial, only two-thirds of the respondents was aware of the study results. Within this group, early initiation of PN was de-implemented completely in 12% of the PICUs, while 40% asserted partial de-implementation. Increasing the awareness, addressing the intervention-specific questions and more frequently revising international guidelines might help to accelerate de-implementation of ineffective, unproven or harmful healthcare.

INTRODUCTION

Optimal nutrition is considered essential to improve outcome in the paediatric intensive care unit (PICU) but large well-designed randomised, controlled trials (RCTs) with clinically relevant outcome measures are lacking.[68,69] The limited evidence leads to a wide variation in nutritional practices between individual intensivists, PICUs and countries. This variation includes timing of and thresholds for the initiation of parenteral nutrition (PN), as measured by a worldwide survey with a point-prevalence.[67] According to this survey completed in 2014, in 20% of the PICUs, PN was initiated within 24 hours after admission, and in 55% of the PICUs within 48 hours.[67] The international guidelines at that time were based on small studies with surrogate outcome measures, observations, and expert opinion, and could not provide clear recommendations on the timing of initiating PN in critically ill children.[103,104] In 2016, the results of the large, international, multicentre RCT 'PEPaNIC' (Paediatric Early versus Late PN in Critically Illness) were published.[18] This RCT showed that administering PN within 24 hours after PICU admission (Early-PN; the standard therapy) was clinically inferior to withholding PN during the first week of PICU admission (Late-PN).[18] Withholding PN during the first week prevented new infections, shortened intensive care dependency, the duration of mechanical ventilation and hospital stay. Based on the impact of these findings, and the scarcity of evidence for the early use of PN in PICUs, one could expect that currently, initiation of supplemental PN is delayed until after the first week of critical illness in the majority of PICUs.

De-implementation or de-adoption is described as 'reducing or stopping low-value, ineffective, harmful or unproven care'.[105-107] However, rational and quantitative evidence are only part of the driving forces for decision making and only 49% of the interventions is supported or contradicted by the available evidence.[105,108] Little is known about the factors that influence the extend and pace of de-implementation.[106,109] Moreover, currently, only 10% of the de-implementation research has focused on paediatric healthcare.[107]

In this study, we explored the degree of early de-implementation of initiating PN in the first week in PICUs and barriers for de-implementation with a survey among physicians and dieticians across PICUs worldwide.

MATERIALS AND METHODS

This electronic (LimeSurvey GmbH version 2.06lts) cross-sectional survey was conducted between May and October 2017. It consisted of 41 questions and was provided in English, French and Spanish. The full questionnaire used for this survey can be found as online supplement to this article (Appendix). In brief, the survey was developed to collect information in different echelons. The first part collected general information of the respondents and responding PICUs, the second part focused on the current practice of PN in the responding PICU, and the third part investigated the awareness of the results of the PEPaNIC trial. Subsequently, the respondents who had read the findings of this study prior to our survey were requested to participate in the final part of the survey in which they were

asked to grade the quality of evidence of the PEPaNIC trial according to the Scottish Intercollegiate Guidelines Network (SIGN) system that was provided in the survey.[110] Finally, they were asked whether and how the PEPaNIC results has changed the current practice of initiating PN in their PICU, and which factors have influenced the degree of de-implementation in their PICU.

The survey was piloted by independent clinicians in two different centres (Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands and the University Hospital of Leuven, Belgium) to test the clarity, relevance and clinical sensibility of the questionnaire, and the questionnaire was adapted accordingly. Data from this pilot were not included in the final analyses and survey results. The survey was electronically distributed among members of the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS) by newsletter and Twitter, and to specific members of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). Reminders were sent three times with six-week intervals. If more than one questionnaire was present for a PICU, the answers were weighed by the inverse of the number of completed questionnaires per centre in order to process conflicting statements within one PICU, without disrupting the weight of the answers per PICU.

Main outcome was the degree of de-implementation (fidelity), with complete de-implementation defined as withholding PN until day 8 of PICU admission. Partial de-implementation was defined as postponed initiation of PN (but still initiated prior to day 8 in PICU) and/or decreased amount of PN as compared with nutritional practices before the results from PEPaNIC, or only administering PN during the first week in specific patient groups. Secondary outcomes were supporting factors and barriers for de-implementation.

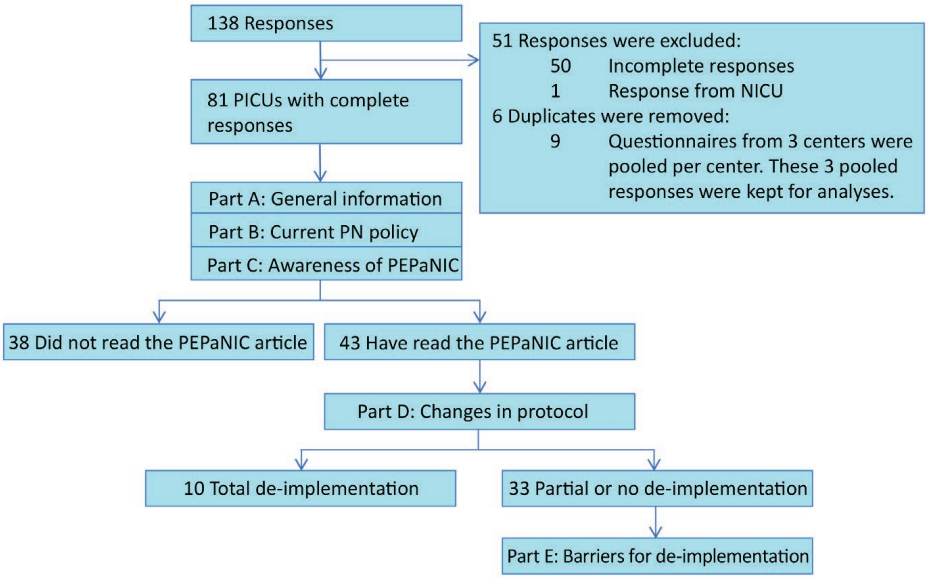
Statistical analysis was performed using IBM SPSS statistics version 24. All answers were categorical, and were expressed as numbers and proportions.

RESULTS

Response

Since the survey was distributed via Twitter, ESPNIC and WFPICCS, with unknown number of PICUs in their databases, the exact number of invited PICUs is unknown. A total of 88 completed questionnaires were received, of which one was removed because the respondent worked in a Neonatal Intensive Care Unit. From the remaining 87 questionnaires, the answers of nine respondents from three centres needed to be pooled per centre by weighing the answers according to the number of completed questionnaires per centre. The 3 pooled responses per centre were kept for analyses, and the individual responses were removed (Figure 1). Finally, responses from 81 PICUs in 39 countries on 6 continents were analysed (Figure 2). Of the respondents, 74% were (paediatric) intensivists, 12% were dieticians or nutritionists, 6% were paediatricians, 5% were nurses or nurse practitioners, and 3% were anaesthesiologists.

Figure 1: Flowchart of the responses and build-up of the survey



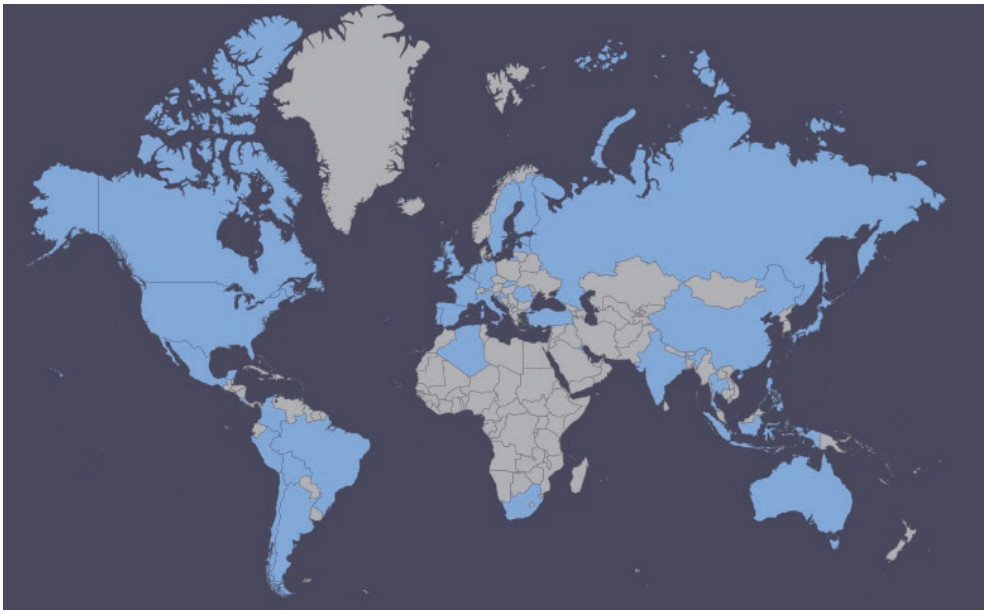
NICU = neonatal intensive care unit; PN = parenteral nutrition.

Of the responding PICUs, 39 (48%) were located in Europe, 14 (17%) in South America, 12 (15%) in North America, and 12 (15%) in Asia (Table 1). The majority of the PICUs had 251-750 paediatric admissions per year (Table 1). All PICU demographics are displayed in table 1.

Current PN practices in PICUs

In 50 of the 81 PICUs (62%), a nutritional protocol regarding PN was present. Most of the protocols were based on international guidelines (27 of 50, 54%), 8 of 50 (16%) on national guidelines, and 15 of 50 (30%) on the opinion of the staff. Respondents from 10 of the 81 PICUs (12%) would always start PN if enteral nutrition (EN) is insufficient, and 4 (5%) would never start PN. In 43 of the 81 PICUs (53%), supplemental PN would be started if enteral nutrition covered less than 80% of the target goals, at 20 (25%) of the PICUs if EN covered less than 50%, and 4 (5%) of the PICUs handled another threshold. PN administration via peripheral intravenous access was possible in 58 of the 81 PICUs (72%).

Figure 2: Participating PICUs: 81 responses from 39 countries (in blue), covering six continents



Created with: https://www.amcharts.com/visited_countries/

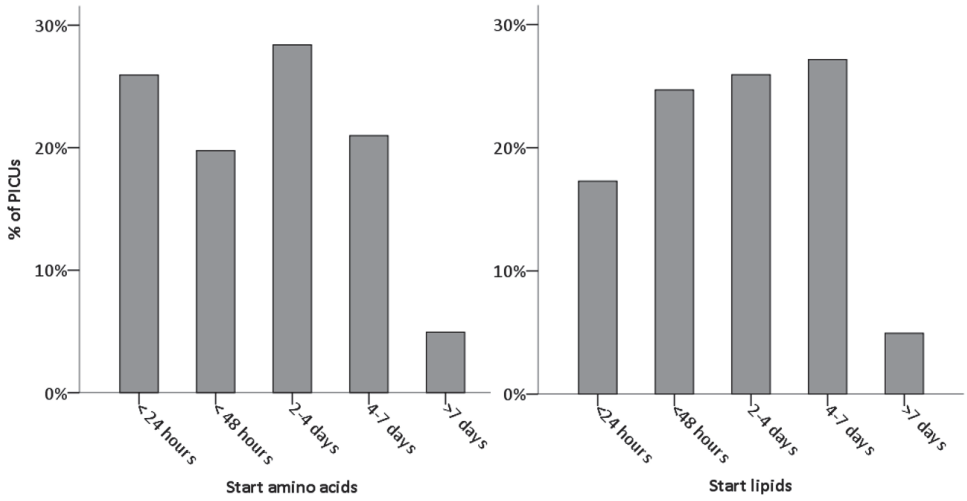
Regarding the timing of PN initiation, amino acids would be started within 48 hours when a child was (expected to be) intolerable to EN in 37 of the 81 PICUs (46%). Initiation of amino acids was postponed beyond the first week in 4 of the 81 PICUs (5%; Figure 3). Lipids would be started within 48 hours in 34 of the 81 PICUs (42%; Figure 3). Lipids would be initiated beyond the first week in 4 of the 81 PICUs (5%; Figure 3). Targeted glucose intake during the first 12-24 hours varied between 1-4 mg/kg/min and 8-10 mg/kg/min. In most cases, 4-6 mg/kg/min was targeted in children who weighed less than 10 kilograms (38 of 81 PICUs, 47%), 1-4 mg/kg/min in children who weighed 10-30 kilograms (50 of 81 PICUs, 62%) and also in children weighing more than 30 kilograms (62 of 81 PICUs, 77%). Of the 81 respondents, 73 (90%) would administer vitamins and trace elements routinely.

Table 1: Characteristics of the responding paediatric intensive care units

Characteristic	No. of PICUs (n=81)
Continent	
Europe	39 (48%)
South America	14 (17%)
Asia	12 (15%)
North America	12 (15%)
Africa	2 (3%)
Oceania	2 (3%)
Hospital type	
University children's hospital	37 (46%)
University hospital	24 (30%)
General hospital	18 (21%)
Other	2 (3%)
Type of PICU	
Multidisciplinary/mixed	75 (93%)
Medical	4 (5%)
Cardiac	1 (1%)
Surgical	1 (1%)
Combination of PICU	
Not combined	66 (82%)
With neonatal ICU	10 (12%)
With adult ICU	4 (5%)
With adult and neonatal ICU	1 (1%)
Size of PICU	
1-10 beds	33 (41%)
11-20 beds	28 (35%)
21-30 beds	16 (50%)
>30 beds	4 (6%)
Paediatric admissions (patients/year)	
1-250	7 (9%)
251-500	29 (36%)
501-750	18 (22%)
751-1000	7 (9%)
1001-1250	7 (9%)
>1250	13 (16%)
Mechanically ventilated patients	
<25 %	9 (11%)
25-50 %	31 (38%)
50-75 %	25 (31%)
>75 %	16 (20%)

PICU = paediatric intensive care unit; ICU = intensive care unit.

Figure 3: Time to initiate parenteral nutrition when enteral nutrition is (expected to be) insufficient



PICU = paediatric intensive care unit.

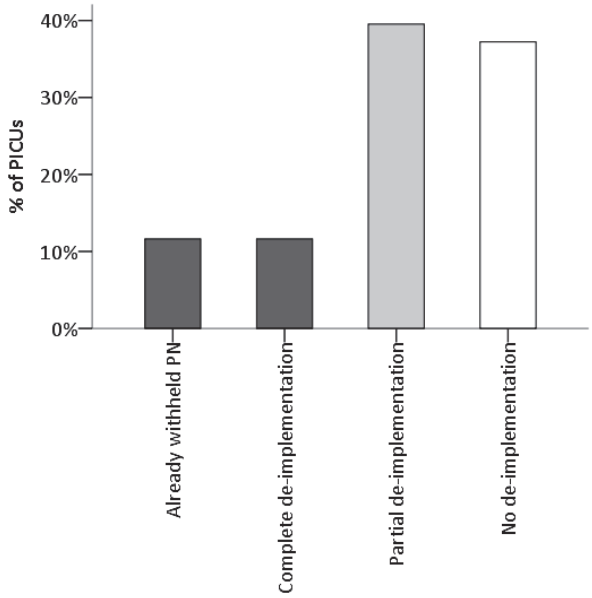
De-implementation of initiating PN early during critical illness

Fifty-three of the 81 respondents (65%) answered to be familiar with the results from the PEPaNIC trial, and 43 (53%) reported to have read the original article. Those who have read the article were larger PICUs and all multidisciplinary/mixed, and reported higher proportions of mechanically ventilated patients (Appendix). The majority of those who have read the article would start PN if EN was <50%, whereas the majority of those who have not read the article would start PN if EN was <80% of target (Appendix). Furthermore, those who have read the article would start amino acids more often within 48 hours than those who did not read the article (Appendix).

Of the 43 respondents who have read the article, 9 (21%) interpreted the level of evidence of the PEPaNIC trial as level 1, 25 (58%) as level 2, and 9 (21%) as level 3. Furthermore, 8 (19%) of these 43 respondents interpreted the grade of recommendation as A (shall be recommended), 17 (39%) as B (should be recommended), and 18 (42%) as 0 (can/may be recommended). These 43 respondents all completed the final part of the survey questions on de-implementation of early PN initiation in their PICU (Figure 1). Complete de-implementation of early PN initiation, due to the results of PEPaNIC, was reported by 12% (5 of 43) and another 5 (12%) declared to already withhold PN during the first week prior to PEPaNIC (Figure 4). Partial de-implementation was asserted by 17 (40%) of the respondents (Figure 4). Of these 17 respondents, 16 reported to give PN during the first week only in specific patient groups (11 to neonates, 11 to undernourished children, and 4 to other, unspecified patients), and 3 respondents declared to have postponed the timing of initiation and/or decreasing the amount of amino acids or lipids. Sixteen (37%) of the 43 PICUs reported

no de-implementation, and continued to administer PN early during PICU admission. Ten of these PICUs would start PN within 48 hours after admission, of which 6 within 24 hours.

Figure 4: De-implementation of parenteral nutrition during the first week of paediatric critical illness



PICU = paediatric intensive care unit; PN = parenteral nutrition.

Associations between PICU/respondent characteristics and de-implementation

The degree of de-implementation within the characteristics of the PICUs/respondents is described in table 2. Higher proportions of complete de-implementation were observed in PICUs from which the respondent rated the level of evidence and grade of recommendation high as compared with those PICUs who rated them lower (Table 2).

Table 2: Distribution of the degree of de-implementation within the characteristics of the 43 PICUs/respondents who have answered part D of the questionnaire

Characteristic	No de-implementation	Partial de-implementation	Complete de-implementation	Already withheld PN
Continent				
Europe	2 (9%)	8 (36%)	8 (36%)	2 (9%)
South America	2 (25%)	4 (50%)	0 (0%)	2 (25%)
Asia	2 (100%)	0 0%)	0 (0%)	0 (0%)
North America	3 (39%)	3 (38%)	1 (13%)	1 (13%)
Africa	1 (50%)	1 (50%)	0 (0%)	0 (0%)
Oceania	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Combination of PICU				
Not combined	14 (40%)	15 (43%)	3 (9%)	3 (9%)
With neonatal ICU	2 (40%)	2 (40%)	0 (0%)	1 (20%)
With adult ICU	0 (0%)	0 (0%)	2 (67%)	1 (33%)
With adult and neonatal ICU	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Size of PICU				
1-10 beds	5 (42%)	4 (33%)	1 (8%)	2 (7%)
11-20 beds	5 (31%)	6 (38%)	3 (19%)	2 (13%)
21-30 beds	6 (50%)	5 (42%)	1 (8%)	0 (0%)
>30 beds	0 (0%)	2 (67%)	0 (0%)	1 (33%)
Experience of respondent (years)				
1-5	0 (0%)	3 (50%)	2 (33%)	1 (17%)
6-10	5 (71%)	2 (29%)	0 (0%)	0 (0%)
11-20	6 (46%)	3 (23%)	1 (8%)	3 (23%)
>20	5 (29%)	9 (53%)	2 (12%)	1 (6%)
Nutritional protocol present				
Yes	12 (41%)	10 (35%)	4 (14%)	3 (10%)
No	2 (29%)	7 (50%)	1 (7%)	2 (14%)
Rated level of evidence				
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3	7 (78%)	2 (22%)	0 (0%)	0 (0%)
2	7 (28%)	11 (44%)	2 (8%)	5 (20%)
1	2 (22%)	4 (44%)	3 (33%)	0 (0%)
Rated grade of recommendation				
Good Practice Points	0 (0%)	0 (0%)	0 (0%)	0 (0%)
0	10 (56%)	6 (33%)	0 (0%)	2 (11%)
B	3 (18%)	9 (53%)	2 (12%)	3 (18%)
A	3 (38%)	2 (25%)	3 (38%)	0 (0%)

PICU = paediatric intensive care unit; ICU = intensive care unit; PN = parenteral nutrition.

Table 3: Barriers for de-implementation (>1 answer per PICU possible) in the 33 PICUs that have partially or not de-implemented early administration of PN

Barrier	No of PICUs (n=33)
Safety issues	
Not convinced of the safety and/or efficacy in undernourished children	17
Convinced that critically ill children need amino acids in the acute phase of illness	15
Not convinced of the safety and/or efficacy in neonates	11
Convinced that critically ill children need lipids in the acute phase of illness	6
Not convinced of the safety in general	4
Convinced that critically ill children need more glucose in the acute phase of illness	2
Confirmation of results	
Waiting for replicating studies	11
Waiting for updated international guidelines [a]	11
Waiting for long-term results	8
Don't consider these results to be cost-effective	1
Structural reasons	
Non-consensus within staff	9
Other [b]	5
Lack of nutritional protocol	2
Because of logistic reasons (i.e. arrangements with pharmacy)	1
Total number of reasons	**103**

PICU = paediatric intensive care unit; PN = parenteral nutrition.

[a] Respondents from Europe: n=7, North America: n=2, South America: n=2 and Africa: n=1.

[b] Provided answers: the PEPaNIC results are not generalizable to our PICU: n=3; PN is administrated rarely in our centre: n=1; we are currently changing our PN strategies: n=1.

Barriers for de-implementation

As familiarity of study results are a condition of studying de-implementation, we started off with making this distinction. Of the respondents, only 65% was familiar with the PEPaNIC study and only 43 (53%) had actually read the article. Of these 43, 33 respondents reported no or partial de-implementation and were asked for reasons not to adopt withholding PN during the first week (Figure 1). The most distinct arguments were those that addressed the safety of postponing PN. The perception that withholding PN would be harmful to children who were undernourished on admission (barrier for 17 respondents, 52%) and neonates (barrier for 11 respondents, 33%) were important barriers. Another major concern was the conviction that parenteral amino acids should be provided during the acute phase of critical illness (mentioned by 15 respondents, 46%). Further arguments represented the need for additional confirmation of the results from the PEPaNIC trial: waiting for replicating studies (11 respondents; 33%), waiting for updated international guidelines (11 respondents; 33%), and waiting for long-term outcomes (8 respondents; 24%) (Table 3). Interestingly, 9 (27%) respondents reported that the results from the PEPaNIC trial were discussed within their staff but this had not led to de-implementation of early PN initiation because of lack of consensus (Table 3).

DISCUSSION

This survey showed that nutritional practices continue to vary greatly among PICUs worldwide as was previously reported.[67] Despite the dearth of evidence in the field of nutritional support in the PICU, in the current survey only about two-thirds of the respondents asserted to be familiar with the results from the PEPaNIC trial and approximately half had read the article. Among these respondents, PN was completely withheld during the first week in almost a quarter of the PICUs, and most PICUs had partially de-implemented early PN initiation, which meant predominantly that early PN would only be given to specific patient groups. Reported barriers for de-implementation were predominantly based on the conviction that PN during the first week of critical illness is necessary in neonates and undernourished children, and especially amino acids were viewed to be essential.

Although this de-implementation rate might be considered low, it is to be expected given the relative short time between publication of PEPaNIC and the survey (approximately 1 year). It has been shown that it takes more than a decade from publication to implementation into practice.[111,112] An important first step in this process is to create awareness of new insights.[113] Interestingly, our survey pointed out that even if the existing evidence in the field is scarce and new results from a large, international study are published in a high-impact, open access journal, only two-thirds of the PICUs was aware of these results.

Besides awareness of new results, (de-)implementation depends on inhibiting and supporting factors. Previous studies have identified the following influences: believe in the benefits for the targeted population, financial implications, organizational structure, caregiver's motivation to change current practice, feasibility, quality of the evidence, credibility of the working group, relevance and generalizability of the research.[114-117] Indeed, most of these factors were mentioned in our survey as arguments not to change current practice. We will discuss those barriers/facilitators that could guide us to enhance early de-implementation.

In our survey, 76% still administered PN during the first week to all critically ill children or specific patient groups, because they believed in the benefit of early initiation of PN. Despite the fact that early-PN appeared to be even more harmful in neonates than in older children, and more harmful in children at the highest risk of malnutrition, as was already reported in the PEPaNIC article,[18] neonates and undernourished children were predominant barriers. After the survey, additional detailed subgroup analyses of neonates and undernourished children were published, which showed that withholding PN was clinically beneficial in these patients as well.[118,119] Concerns on withholding PN in critically ill children might be explained by several assumptions. Since undernourishment on admission has been associated with worse clinical outcomes, it is assumed that providing (parenteral) nutrition can improve clinical outcomes by promoting anabolism. In small RCTs, higher provision of energy and protein/amino acids resulted in a positive protein balance.[3,120] Subsequently, it was assumed that this would also lead to improved clinical outcomes. These assumptions regarding PN might have reduced the faith in the controversial results from the PEPaNIC study,

which is also reflected in a number of respondents who requested for repeat studies. Currently, we could identify one single centre RCT on ClinicalTrials.gov, which is designed to randomize 80 critically ill children to receive supplemental PN within 12 or 96 hours after admission.[121] However, for clinicians working in combined adult/paediatric ICUs, PEPaNIC could have been considered as a repeat study. Withholding PN for a week in critically ill adults has been included in the 'choosing wisely campaign', a list made by specialty societies of possible unnecessary healthcare recommendations.[122] This might explain why PN was completely withheld in critically ill children during the first week in all of the combined adult/paediatric ICUs. Additionally, since evidence for withholding PN during the first week in critically ill adults has already been published first in 2011,[123] the time between evidence from research and de-implementation in practice might play a role. Furthermore, a significant proportion of the respondents mentioned the request for updated guidelines. When the survey was distributed, the most recent international guidelines were developed in 2005 and 2009. In the meantime, these guidelines have been updated by the leading expert nutrition societies,[74,99] which means that the time between previous and current versions of the guidelines was 8 to 13 years. The fact that updated guidelines were awaited by a significant proportion of respondents stresses the importance of up-to-date guidelines. Hence, more frequent updates of the international guidelines might enhance (de-)implementation.

Despite the factors that hamper de-implementation, we have observed a shift in the timing of initiation of PN in critically ill children. In 2013, a worldwide survey was conducted, addressing nutritional practices in the PICU.[67] In this survey, the majority (55%) of the PICUs reported to start PN within 48 hours, and 20% within 24 hours. Furthermore, PN was completely withheld in only 3.5% of the PICUs before the PEPaNIC results were published.[67] Comparing these results to the results of our study, there seems to be a shift towards initiation of PN between day 2 to 7 and an increase in complete de-implementation of early PN, although this cannot be concluded confidently as the responding PICUs were not exactly the same.

Limiting the delay in de-implementation is of particular importance in case of harm by an intervention – which was the case in early-PN – or cost-ineffectiveness. Based on our results and existing literature, de-implementation might be accelerated by increasing awareness, gaining trust on the efficacy and safety of stopping the intervention, and facilitating up-to-date international guidelines. An important aspect to take into account is that the personal willingness and readiness to change a practice differs widely, which is illustrated by the 'theory of the diffusion of innovation' by Rogers et al.[113] According to this theory, the PICUs who had de-implemented early PN in our survey could be the 'Early Adopters', who generally have the highest degree of opinion leadership.[113] Hence, the next step to increase awareness and gain support, demands the Innovators and Early Adopters to distribute the knowledge within their networks. Furthermore, the concerns on the efficacy and safety of stopping the intervention (in our case withholding PN) should be addressed if possible. Since the launch of this survey, several secondary analyses have investigated the main concerns, such as the harm associated with administration of amino acids,[70] the efficacy and safety of withholding PN in

undernourished children[119] and neonates,[118] the long-term effects on physical and neuropsychological functions,[124] and the cost-effectiveness of withholding PN.[125] All these new findings were supportive for de-implementation of early-PN. Additionally, underlying mechanisms are currently explored.[126] Finally, since many clinical practices depend on the international opinion, de-implementation might be accelerated if the international guidelines would be revised more frequently in order to cover the most up-to-date evidence.

The strength of our study is the widespread responses worldwide. However, some limitations should also be addressed. First, responses from 81 PICUs are a small fraction of all PICUs worldwide. Possibly, only physicians interested in nutrition might have responded to our survey, which poses a risk of selection bias. Second, some answers from the respondents could potentially have been socially desirable, as this survey has been conducted by the PEPaNIC study group. Furthermore, some respondents gave inconsistent answers. We have analysed all answers as provided by the respondent to avoid incorrect interpretation. And third, with this survey, we have measured theoretical de-implementation based upon the answers of the respondents, without measuring real PN practices. A previous survey addressing nutritional practices in PICUs, in which the questionnaire was followed by a point-prevalence, illustrated that the respondents often overestimated their practices.[67]

CONCLUSIONS

One year after the publication of the PEPaNIC trial, only two-thirds of the respondents was aware of the study results. Within this group, complete de-implementation of starting PN in the first week of critical illness was done in 12% of the PICUs worldwide, and partial de-implementation was done in 40% of the PICUs. Another 12% of PICUs already withheld PN during the first week. Important barriers for not de-implementing early PN were concerns on the efficacy and safety of withholding PN, and waiting for updated international guidelines. Increasing the awareness, addressing the intervention-specific questions and more frequently revising the international guidelines might help to accelerate de-implementation of ineffective, unproven or harmful healthcare.

APPENDIX

Supplementary Methods 1: Questionnaire

Part A: General information

1. What is your country of work?
2. What is the name of your institution?
3. What type of hospital do you work in?
   - □ general
   - □ university
   - □ university-children's
   - □ other, specify
4. What is your profession?
   - □ (paediatric) intensivist
   - □ anaesthesiologist
   - □ paediatrician
   - □ surgeon
   - □ dietician/nutritionist
   - □ nurse/nurse practitioner
   - □ other, specify
5. How many years of experience do you have working in a PICU?
   - □ 1-5
   - □ 6-10
   - □ 11-20
   - □ >20
6. What type of a PICU do you work in?
   - □ multidisciplinary/mixed
   - □ surgical
   - □ cardiac
   - □ medical
   - □ other, specify
7. Is the PICU combined with an adult ICU or a neonatal ICU?
   - □ not combined
   - □ neonatal
   - □ adult
   - □ Both neonatal and adult
8. What is the number of paediatric ICU beds in your unit (until age 18 years)?
   - □ 1-10
   - □ 11-20
   - □ 21-30
   - □ >30
9. What is the average number of paediatric admissions per year in your unit (until age 18 years)?
   - □ 1-250
   - □ 251-500

□ 501-750
□ 751-1000
□ 1001-1250
□ >1250

10. What is the average proportion of mechanically (invasive) ventilated paediatric patients per year in your unit (until age 18 years)?
□ <25%
□ 25-50%
□ >50-75%
□ >75%

Part B: Parenteral nutrition in your PICU

Please fill in your <u>current practice</u> regarding PN for critically ill paediatric patients.

1. Is there a nutritional protocol regarding PN used in your PICU?
Yes / No
If Yes → after C, answer D1
If No → after C, answer D2
2. What is the basis of your nutritional protocol?
□ International guideline → go to B3
□ National guideline → go to B4
□ Opinion of the staff → go to B4
3. Which guideline?
□ European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)
□ American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)
□ Adult international guideline
4. How much glucose is administered during the first 12-24 hours of admission:
- <10 kg □ 1-4 mg/kg/min (1.4-5.8 g/kg/day) □ 4-6 mg/kg/min (5.8-8.6 g/kg/day) □ 6-8 mg/kg/min (8.6-11.5 g/kg/day) □ 8-10 mg/kg/min (11.5-14.4 g/kg/day)
- 10-30 kg □ 1-4 mg/kg/min (1.4-5.8 g/kg/day) □ 4-6 mg/kg/min (5.8-8.6 g/kg/day) □ 6-8 mg/kg/min (8.6-11.5 g/kg/day) □ 8-10 mg/kg/min (11.5-14.4 g/kg/day)
- >30 kg □ 1-4 mg/kg/min (1.4-5.8 g/kg/day) □ 4-6 mg/kg/min (5.8-8.6 g/kg/day) □ 6-8 mg/kg/min (8.6-11.5 g/kg/day) □ 8-10 mg/kg/min (11.5-14.4 g/kg/day)
5. At what point would you start amino acids in a child (expected to be) intolerable to enteral feeds?
□ < 24 hours
□ < 48 hours
□ 2-4 days
□ 4-7 days
□ >7 days
6. At what point would you start lipids in a child (expected to be) intolerable to enteral feeds?
□ < 24 hours
□ < 48 hours

- □ 2-4 days
- □ 4-7 days
- □ >7 days

7. When enteral nutrition is provided but is insufficient to meet target goals, would PN be added?
   - □ No
   - □ Yes, always
   - □ Yes, if enteral nutrition covers < 80% of target calories
   - □ Yes, if enteral nutrition covers < 50% of target calories
   - □ Other
8. If PN is given in combination with enteral nutrition: at what moment (percentage of nutritional target achieved by enteral nutrition) is PN stopped?
   - □ If enteral nutrition covers 100% of target calories
   - □ If enteral nutrition covers > 80% of target calories
   - □ If enteral nutrition covers > 50% of target calories
   - □ Other
9. How is PN provided in your institution?
   - □ Pharmacy-customised, age/weight specific
   - □ Commercial mixed bags
   - □ Other
10. Is it possible to administer PN without a central venous line? Yes / No
11. Do you routinely administer vitamins and trace elements? Yes / No

Part C: Awareness of the Early versus Late PN in Critically Ill Children (PEPaNIC) study

The results of the international, multicentre, randomised, controlled trial Paediatric Early versus Late Parenteral Nutrition in Critical Illness (PEPaNIC) have been published in the New England Journal of Medicine in March 2016.

1. Are you familiar with the results of this study? Yes / No
2. Did you read this article before you filled out this survey? Yes / No
3. Did you read the supplemental material before you filled out this survey? Yes / No
4. How would you rate the level of evidence?
   - □ 1 (high to excellent)
   - □ 2 (moderate to high)
   - □ 3 (low)
   - □ 4 (expert opinion)
5. How would you rate the grade of recommendation?
   - □ A (shall be recommended)
   - □ B (should be recommended)
   - □ 0 (can/may be recommended)
   - □ GPP (Good Practice Points)

Part D1: Change in Nutritional Practice

In the PEPaNIC study, in children who were allocated to the Late-PN group, during the first week of critical illness, PN was withheld completely (meaning: low amounts of glucose (<2 mg/kg/min), no

amino acids and no lipids were administered). Late-PN resulted in lower percentage of new infections and shorter duration of PICU stay compared to Early-PN.

1. Has the local nutritional protocol of your PICU, concerning the initiation or amount of PN, been changed due to the results of this study?
    - □ **No** change. We already withheld PN during the first week → go to D9, after D: go to E4
    - □ **No** change. We still administer PN during the first week in all children → go to D9
    - □ **Yes**, we have changed our practice. We now withhold PN during the first week → go D6 & D8, after D: go to E4
    - □ **Yes**, we have changed our protocol <u>partially</u> or only in specific patients. We withhold or decreased component(s) of PN → go to D2
2. Please specify: during the first week of critical illness in children… (multiple choice)
    - □ We still administer PN in the first week <u>only</u> in specific patient groups (i.e. neonates, malnourished children, specific diseases) → go to D3
    - □ We withhold or decrease only some of the macronutrients (glucose, amino acids, lipids) → go to D5
    - □ Other, namely …. → go to D5
3. Which patient group(s) continued receiving PN during the first week? (multiple choice)
    - □ neonates (<1 month)
    - □ malnourished children
    - □ other
4. At which day was/is PN started in this patient group?

    Neonates:
    - □ < 24 hours
    - □ < 48 hours
    - □ 2-4 days
    - □ 4-7 days
    - □ >7 days

    Malnourished children:
    - □ < 24 hours
    - □ < 48 hours
    - □ 2-4 days
    - □ 4-7 days
    - □ >7 days

    Other:
    - □ < 24 hours
    - □ < 48 hours
    - □ 2-4 days
    - □ 4-7 days
    - □ >7 days

    → go to D9
5. Did you change the administration of parenteral amino acids during the first week due to the results of this study? (multiple choice)
    - □ No → go to D7

- ☐ Yes, we have changed the timing of initiation of amino acids → go to D6
- ☐ Yes, we have changed the amount of amino acids → go to D7

6. At which day were amino acids started before the change in protocol:

- ☐ < 24 hours
- ☐ < 48 hours
- ☐ 2-4 days
- ☐ 4-7 days
- ☐ >7 days

7. Did you change the administration of parenteral lipids during the first week due to the results of this study? (multiple choice)

- ☐ No → go to D9
- ☐ Yes, we have changed the timing of initiation of lipids → go to D8
- ☐ Yes, we have changed the amount of lipids → go to D9

8. At which day were parenteral lipids started before the change in protocol:

- ☐ < 24 hours
- ☐ < 48 hours
- ☐ 2-4 days
- ☐ 4-7 days
- ☐ >7 days

9. Did you lower the amount of glucose administered intravenously during the first week due to the results of this study? Yes / No

10. Keeping the results of the study in mind, when a child deteriorates clinically after the first week (i.e. sepsis), would you then discontinue PN? Yes / No.

Part D2: Change in Nutritional Practice

In the PEPaNIC study, in children who were allocated to the Late-PN group, during the first week of critical illness, PN was withheld completely (meaning: low amounts of glucose (<2 mg/kg/min), no amino acids and no lipids were administered). Late-PN resulted in lower percentage of new infections and shorter duration of PICU stay compared to Early-PN.

1. Has the local nutritional practice of your PICU, concerning the initiation or amount of PN, been changed due to the results of this study?

- ☐ **No** change. We already withheld PN during the first week → go to D9, after D: go to E4
- ☐ **No** change. We still administer PN during the first week in all children → go to D9
- ☐ **Yes**, we have changed our practice. We now withhold PN during the first week → go D6 & D8, after D: go to E4
- ☐ **Yes**, we have changed our practice partially or only in specific patients. We withhold or decreased component(s) of PN → go to D2

2. Please specify: during the first week of critical illness in children… (multiple choice)

- ☐ We still administer PN in the first week only in specific patient groups (i.e. neonates, malnourished children, specific diseases) → go to D3
- ☐ We withhold or decrease only some of the macronutrients (glucose, amino acids, lipids) → go to D5
- ☐ Other, namely …. → go to D5

3. Which patient group(s) continued receiving PN during the first week? (multiple choice)
   - □ neonates (<1 month)
   - □ malnourished children
   - □ other

4. At which day was/is PN started in this patient group?

   Neonates:
   - □ < 24 hours
   - □ < 48 hours
   - □ 2-4 days
   - □ 4-7 days
   - □ >7 days

   Malnourished children:
   - □ < 24 hours
   - □ < 48 hours
   - □ 2-4 days
   - □ 4-7 days
   - □ >7 days

   Other:
   - □ < 24 hours
   - □ < 48 hours
   - □ 2-4 days
   - □ 4-7 days
   - □ >7 days

   → go to D9

5. Did you change the administration of parenteral amino acids during the first week due to the results of this study? (multiple choice)
   - □ No → go to D7
   - □ Yes, we have changed the timing of initiation of amino acids → go to D6
   - □ Yes, we have changed the amount of amino acids → go to D7

6. At which day were amino acids started <u>before</u> the change in practice:
   - □ < 24 hours
   - □ < 48 hours
   - □ 2-4 days
   - □ 4-7 days
   - □ >7 days

7. Did you change the administration of parenteral lipids during the first week due to the results of this study? (multiple choice)
   - □ No → go to D9
   - □ Yes, we have changed the timing of initiation of lipids → go to D8
   - □ Yes, we have changed the amount of lipids → go to D9

8. At which day were parenteral lipids started <u>before</u> the change in practice:
   - □ < 24 hours
   - □ < 48 hours
   - □ 2-4 days

- 4-7 days
- >7 days

9. Did you lower the amount of glucose administered intravenously during the first week due to the results of this study? Yes / No

10. Keeping the results of the study in mind, when a child deteriorates clinically after the first week (i.e. sepsis), would you then discontinue PN? Yes / No.

Part E: Reasons for not implementing Late-PN

1. What is/are reason(s) for not withholding PN in your PICU during the first week of critical illness in children? (multiple choice)

- waiting for replicating studies
- not convinced of the safety
- not convinced of the safety and/or efficacy in neonates
- not convinced of the safety and/or efficacy in malnourished children
- convinced that critically ill children need amino acids in the acute phase of illness
- convinced that critically ill children need more glucose in the acute phase of illness
- convinced that critically ill children need lipids in the acute phase of illness
- waiting for long-term results.
- don't consider these results to be cost-effective
- waiting for updated international guidelines
- lack of nutritional protocol
- non-consensus within staff
- Because of logistic reasons (i.e. arrangements with pharmacy) (→ go to E2)
- Other, namely …..

All answers (except logistic reasons)→go to E4

2. When enteral nutrition is insufficient to meet nutritional targets, do you intend to withhold PN during the first week of critical illness in the future?

- No, I intend to start PN as soon as possible
- Yes, I intend to withhold PN for less than 7 days in the future (→ go to E3)
- Yes, I intend to withhold PN during the first week in the future (→ go to E4)

3. At which day do you intend to start PN in the future?

- < 24 hours
- < 48 hours
- 2-4 days
- 4-7 days
- >7 days

4. Do you have any comments on this survey? (not mandatory)

5. If you would like to be informed about the results of this survey, please fill in your name and email-address. (not mandatory)

Supplementary Table 1: Characteristics and nutritional practices of PICUs of which the respondent had read the article versus those who have not read the article

Characteristic / nutritional practice	Have read the article (n=43)	Did not read the article (n=38)
Continent		
Europe	22 (51.2%)	17 (44.7%)
South America	8 (18.6%)	6 (15.8%)
Asia	2 (4.7%)	10 (26.3%)
North America	8 (18.6%)	4 (10.5%)
Africa	2 (4.7%)	0 (0%)
Oceania	1 (2.3%)	1 (2.6%)
Hospital type		
University children's hospital	26 (60.5%)	11 (28.9%)
University hospital	10 (23.3%)	14 (36.8%)
General hospital	6 (14.0%)	12 (31.6%)
Other	1 (2.3%)	1 (2.6%)
Type of PICU		
Multidisciplinary/mixed	43 (100%)	32 (84.2%)
Medical	0 (0%)	4 (10.5%)
Cardiac	0 (0%)	1 (2.6%)
Surgical	0 (0%)	1 (2.6%)
Combination of PICU		
Not combined	35 (81.4%)	31 (81.6%)
With neonatal ICU	5 (11.6%)	5 (13.2%)
With adult ICU	3 (7.0%)	1 (2.6%)
With adult and neonatal ICU	0 (0%)	1 (2.6%)
Size of PICU		
1-10 beds	12 (27.9%)	21 (55.3%)
11-20 beds	16 (37.2%)	12 (31.6%)
21-30 beds	12 (27.9%)	4 (10.5%)
>30 beds	3 (7.0%)	1 (2.6%)
Paediatric admissions (patients/year)		
1-250	3 (7.0%)	4 (10.5%)
251-500	13 (30.2%)	16 (42.1%)
501-750	9 (20.9%)	9 (23.7%)
751-1000	4 (9.3%)	3 (7.9%)
1001-1250	5 (11.6%)	2 (5.3%)
>1250	9 (20.9%)	4 (10.5%)
Mechanically ventilated patients		
<25%	6 (14.0%)	3 (7.9%)
25-50%	13 (30.2%)	18 (47.4%)
50-75%	14 (32.6%)	11 (28.9%)
>75%	10 (23.3%)	6 (15.8%)

Supplementary table 1 continued

Characteristic / nutritional practice	Have read the article (n=43)	Did not read the article (n=38)
Add PN if EN is insufficient		
No	2 (4.7%)	2 (5.3%)
Yes, if EN <50%	13 (30.2%)	7 (18.4%)
Yes, if EN <80%	21 (4.7%)	22 (57.9%)
Yes, always	5 (11.6%)	5 (13.2%)
Other	2 (4.7%)	2 (5.3%)
Start amino acids		
<24 hours	12 (27.9%)	9 (23.7)
<48 hours	5 (11.6%)	11 (28.9%)
2-4 days	12 (27.9%)	9 (23.7%)
4-7 days	10 (23.3%)	7 (18.4%)
>7 days	4 (9.3%)	0 (0.0%)
Start lipids		
<24 hours	9 (20.9%)	5 (13.2%)
<48 hours	9 (20.9%)	11 (28.9%)
2-4 days	11 (25.6%)	10 (26.3%)
4-7 days	11 (25.6%)	11 (28.9%)
>7 days	3 (7.0%)	1 (2.6%)

PICU = paediatric intensive care unit; ICU = intensive care unit; PN = parenteral nutrition.

Chapter 3

Early versus Late Parenteral Nutrition in Critically Ill, Term Neonates: a Preplanned Secondary Subgroup Analysis of the PEPaNIC Multicentre Randomised Controlled Trial

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ABSTRACT

Background

Previous randomised studies showed that withholding parenteral nutrition (PN) for 1 week of critical illness was superior to early initiation (<24-48 h) of PN in children and adults. However, neonates are considered more susceptible to macronutrient deficits. We investigated the effect of withholding PN for 1 week in critically ill, term neonates.

Methods

We previously did a randomised, controlled study (PEPaNIC) of children aged up to 17 years admitted to paediatric intensive care units (ICUs) in three hospitals in Belgium, Canada, and the Netherlands randomly assigned (1:1) to either standard care of PN initiated early within 24 hours of admission to an ICU or Late-PN (where supplemental PN was withheld for 1 week after admission to the ICU. In this preplanned, secondary subanalysis of PEPaNIC, we looked at data from critically ill, term neonate participants (gestational age ≥37 weeks) aged up to 28 days (studied in overlapping age groups of ≤4 weeks, ≤1 week, and <1 day— i.e., age at admission). In both the Early-PN and Late-PN groups, enteral nutrition was initiated as soon as possible and increased according to local protocols. Outcome assessors and investigators not directly involved in the paediatric ICU were not informed of treatment allocation. The primary endpoints were incidence of new infections and duration of paediatric ICU dependency (quantified as the number of days in the paediatric ICU and likelihood of earlier live discharge from the ICU), analysed based on intention to treat. Multivariable analyses were adjusted for the following risk factors: centre, Paediatric Logistic Organ Dysfunction score, Paediatric Index of Mortality 2 score, diagnosis group, and weight-for-age Z scores on admission. Secondary safety outcomes were mortality (at 90 days, during the intervention, in the paediatric ICU, and in the hospital) and hypoglycaemic incidents during the intervention. All patients in the respective groups were included in the safety analysis.

Findings

Between June 18, 2012, and July 27, 2015, we included 209 participants in this substudy, 145 of whom were aged up to and including 1 week and 45 aged younger than 1 day. In neonates aged up to and including 4 weeks, Late-PN increased the likelihood of earlier live discharge from the paediatric ICU compared with Early-PN (adjusted hazard ratio [HR] 1.61, 95% CI 1.19–2.20; p=0.0021) but did not affect the risk of infection. The risk of infection in neonates aged up to and including 1 week and younger than 1 day was lower with Late-PN than with Early-PN (adjusted odds ratios [OR] 0.36, 95% CI 0.15–0.83, p=0.017; and 0.10, 0.01–0.64, p=0.015, respectively). For neonates aged up to and including 1 week, the likelihood of an earlier live discharge from the ICU was higher with Late-PN (adjusted HR 1.69, 95% CI 1.16–2.46; p=0.0063). For neonates younger than 1 day, adjusted HR was 1.95 (95% CI 0.93–4.12; p=0.078). Mortality at all studied time-points was similar between the groups for all ages; however, in neonates aged up to and including 4 weeks and aged up to and including 1 week,

the risk of hypoglycaemia was higher with Late-PN (23% vs 14%; adjusted OR 3.05, 95% CI 1.27–7.35, p=0.013; and 24% vs 14%; 3.57, 1.23–10.45, p=0.019, respectively).

Interpretation

In critically ill, term neonates, withholding PN for 1 week was clinically superior to standard care of Early-PN for short-term outcomes. However, withholding PN for 1 week significantly increased the risk of developing hypoglycaemia, which necessitates long-term follow-up of these children before Late-PN can be confidently recommended for this vulnerable patient group.

INTRODUCTION

Findings from recent multicentre, randomised, controlled trials showed that withholding parenteral nutrition (PN) to supplement insufficient enteral nutrition (EN) for patients in the first week in an intensive care unit (ICU) led to better clinical and health-economic outcomes than initiating PN early (<24-48 h), both in adults and in children.[18,123,125,127] Preplanned secondary analyses of these studies suggested that the early administration of amino acids rather than glucose or lipids was associated with the harm caused by early supplementation of PN.[70,128] In these trials, there was an age-dependent effect, with the largest benefit of withholding PN occurring in children and term neonates.[18,123] However, withholding supplemental PN in neonates for a week, especially amino acids, contradicts with current advice.[103] Neonates are susceptible to acquiring macronutrient deficits because of their low stores of glycogen and fat combined with increased energy and protein requirements to sustain growth. Therefore, recommendations for macronutrient intake are higher for neonates than for older children and adults, and early supplementation with PN is often more strongly promoted in neonates than in older children.[103] Concerns raised by experts regarding withholding PN in neonates have primarily focused on the risk of developing hypoglycaemia and amino acid deficits.[71-73]

We previously did a randomised, controlled study (PEPaNIC)[18] that investigated the effect of withholding PN in the first week of intensive care versus early PN within 24 hours on outcomes in children admitted to a paediatric ICU. In this secondary analysis of the PEPaNIC study, we investigated the efficacy and safety of withholding supplemental PN for 1 week in all neonates enrolled in the trial. We analysed the effects on patients aged up to and including 4 weeks, up to and including 1 week, and younger than 1 day. Because of the major concerns raised by experts in the field regarding withholding PN, we further investigated the effect on neonates who did not tolerate any EN during the first week in the paediatric ICU. Finally, we investigated whether early amino acid administration might be associated with harm in neonates as has been observed in children.[70]

METHODS

Study design and participants

PEPaNIC included 1440 critically ill children aged from term newborns (gestational age ≥37 weeks) to 17 years, with a medium-to-high risk of malnutrition who were admitted to three paediatric ICUs in Belgium (Leuven), Canada (Edmonton), and the Netherlands (Rotterdam) from June 18, 2012, to July 27, 2015. The study protocol has been reported previously in detail.[18,129] This preplanned secondary analysis included critically ill, term newborn babies aged up to 28 days who participated in PEPaNIC (Appendix).[18] The institutional ethical review boards of the participating centres in Leuven (ML8052), Rotterdam (NL38772.000.12) and Edmonton (Pro00038098) approved the study. Written informed consent was obtained from participants' parents or legal guardians.

Randomisation and masking

Participants were randomly assigned (1:1) to either withholding supplemental PN for the first week after admission to the paediatric ICU (Late-PN) or to standard care of initiating PN within 24 hours of admission (Early-PN) when EN alone was insufficient. In both groups, EN was initiated as soon as possible and increased according to local protocols. Outcome assessors and investigators not directly involved in the paediatric ICU were not informed of treatment allocation.

Procedures

PN was provided at a dose and of a composition that varied according to local guidelines and was not provided as an all-in-one product. For patients assigned to Early-PN, this was initiated within 24 hours after admission to the paediatric ICU as supplementation if EN provided less than 80% of the target to reach the local age-specific and weight-specific caloric targets. In patients assigned to Late0-PN, PN was withheld during the first week in the ICU. To match the fluid administration of the Early-PN group, taking into account the volume of EN delivered, a mixture of dextrose 5% and saline was provided. To prevent refeeding syndrome, patients from both groups received intravenous micronutrients (trace elements, minerals, and vitamins) early in similar amounts, until EN reached 80% of caloric targets. For patients from both groups who were still in the ICU after a week and who were not yet receiving 80% of the caloric target enterally, PN was administered to reach the targets. If a central venous line was not or was no longer in place for clinical purposes, any required PN was delivered via a peripheral line. Blood glucose control with insulin for neonates differed according to local protocols. In Leuven, insulin infusion was started to target blood glucose concentrations of 2.7-4.4 mmol/L. In Rotterdam, neonates received insulin infusion to target blood glucose concentrations of 4.0-8.0 mmol/L. In Edmonton, patients received insulin infusion when blood glucose concentrations exceeded 10.0 mmol/L. Blood glucose concentrations were checked hourly after every change in macronutrient intake or insulin administration until three consecutive measurements were within the normal range.[18,129] This analysis investigated outcomes in three overlapping age groups (≤4 weeks, ≤1 week, and <1 day). Neonates with no or minimal EN were defined as those who had stayed in the paediatric ICU for at least 7 days, and were unable to receive EN or had only received trophic feeding (<40 mL per day) during the first week, with a maximum of 80 mL per week.

Outcomes

The primary efficacy endpoints were the incidence of infections acquired in the paediatric ICU and duration of paediatric ICU dependency (quantified as the crude number of days in the paediatric ICU and likelihood of earlier live discharge from the ICU). Secondary efficacy outcomes were duration of mechanical ventilation (crude number of days and likelihood of earlier live weaning from ventilation), maximum plasma urea concentration, duration of hospital stay (crude number of days and likelihood of earlier live discharge from hospital), and direct health-care costs.[125] The assessment of infections acquired in the paediatric ICU was

based on an a priori-drafted protocol, which made use of data on prescribed antibiotics and clinical infection and inflammation (appendix).[18,129] ICU dependency was defined as requiring or at-risk for requiring vital organ support. Total direct health-care costs were explored from a hospital perspective in the Belgian and Dutch study populations, because these healthcare systems are reasonably comparable.[125] Secondary safety endpoints were 90-day mortality, death during the first week, mortality in the paediatric ICU, and hospital mortality, as well as incidence of hypoglycaemia (i.e., plasma glucose concentration <40 mg/dL [2.2 mmol/L]). For the patients in Leuven who had an episode of hypoglycaemia, time-to-recovery from hypoglycaemia was also investigated.

Statistical analysis

Data were analysed based on intention to treat for the whole group of neonates aged up to and including 4 weeks and those aged up to and including 1 week. The main outcomes were also analysed separately in neonates younger than 1 day and in neonates who had received no or minimal enteral nutrition during the first week. The original PEPaNIC trial was a priori statistically powered to detect a difference in new infections, as in the adult EPaNIC trial,[123] and stratified for age according to the groups younger than 1 year, and 1 year and older. Because the sample size of the present subanalysis depended on the number of neonates included in PEPaNIC, we did a retrospective power analysis based on observed differences for risk of new infection as primary endpoint, rather than an a-priori sample size calculation.

We reported variables as frequencies (%), mean (SD), or median (IQR) as appropriate, and did univariable and multivariable analyses. The multivariable analyses included logistic and linear regression for dichotomous and continuous outcomes, respectively, and Cox proportional hazard analysis for time-to-event outcomes with data censored at 90 days. A competing risk analysis was used for duration outcomes, with data of non-survivors censored at 91 days. Multivariable analyses were adjusted for the predefined baseline risk factors of centre, Paediatric Logistic Organ Dysfunction (PELOD) score, Paediatric Index of Mortality 2 (PIM2) score, diagnosis group (medical, surgical-cardiac, or surgical other), and weight-for-age Z scores on admission;[130,131] in a sensitivity analysis they were also adjusted for age in neonates aged up to and including 4 weeks. Results are reported as odds ratios (OR), hazard ratios (HR), or beta values (β), and corresponding 95% CI. No corrections were made for multiple testing.

To investigate which macronutrient might be accountable for any potential harm, we did an explanatory analysis in neonates aged up to and including 4 weeks and aged up to and including 1 week of the independent associations between average daily total doses of each macronutrient class (ie, glucose, lipids, and amino acids) up to each of the first 7 days in the paediatric ICU and clinical outcomes with use of multivariable Cox proportional hazard analysis censored at 90 days, adjusted for the predefined baseline risk factors listed earlier. This method has been previously described in detail.[70] Briefly, because PEPaNIC investigated the effect on outcome of Late-PN versus Early-PN over the first 7 days after admission to a paediatric ICU, with doses titrated differently for each macronutrient as crude g/kg per day,

we analysed independent associations between clinical outcomes and average daily total doses of each macronutrient up to each of the 7 days for neonates aged up to and including 4 weeks and aged up to and including 1 week who were still in the ICU on those respective days (Appendix). Associations of each of these average doses with the likelihoods of acquiring a new infection in the ICU (time to first new infection, with left-truncation), earlier live discharge from the ICU, and earlier live weaning from mechanical ventilation were studied. No corrections for multiple comparisons were done. We considered two-sided p values of less than 0.05 as statistically significant for all analyses. Analyses were done with SPSS Statistics v.21 or JMP Pro-13.1. An independent data and safety monitoring board oversaw the original trial.[18]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

RESULTS

Patients

This subanalysis included 209 term neonates aged up to and including 4 weeks (of 917 screened for eligibility), of which 145 neonates aged up to and including 1 week, of which 45 neonates aged younger than 1 day (Appendix). Macronutrient intake per day up to day 7 in the paediatric ICU, illustrating protocol adherence, is in the appendix. In neonates aged up to and including 4 weeks and those aged up to and including 1 week, the PIM2 score was significantly higher in the Early-PN groups than in the Late-PN groups, reflecting a higher risk of mortality (Table 1).

Table 1: Baseline characteristics of the intention-to-treat population

Characteristic	Age ≤4 weeks			Age ≤1 week			Age <1 day		
	Early-PN (n=98)	Late-PN (n=111)	P-value[a]	Early-PN (n=73)	Late-PN (n=72)	P-value[a]	Early-PN (n=28)	Late-PN (n=17)	P-value[a]
Male sex	58 (59%)	62 (56%)	0.63	45 (62%)	39 (54%)	0.36	20 (71%)	10 (59%)	0.38
Age at randomisation (days)	2 (0-8)	3 (1-13)	0.036	1 (0-3)	2 (1-3)	0.26	-	-	-
Gestational age (weeks)	38.4 (1.35)	38.6 (1.55)	0.23	38.3 (1.2)	38.7 (1.4)	0.10	38.3 (0.84)	37.6 (1.00)	0.022
Birth weight (g)	3193 (538)	3238 (510)	0.54	3162 (496)	3193 (496)	0.70	3109 (504)	3065 (424)	0.83
Weight-for-age Z-score[b]	-0.43 (1.18)	-0.46 (1.07)	0.83	-0.29 (1.06)	-0.35 (1.05)	0.75	-0.40 (1.03)	-0.17 (0.91)	0.32
PELOD score	12.5 (12-32)	12 (12-31)	0.19	13 (12-32)	12 (12-22)	0.067	12 (12-21)	12 (12-12)	0.010
PIM2 score	-1.71 (1.79)	-2.30 (1.77)	0.016	-1.63 (1.87)	-2.33 (1.77)	0.021	-1.74 (1.79)	-2.35 (1.89)	0.28
Risk of mortality (%)[c]	9.9 (4.8-41.7)	6.7 (3.0-20.4)	0.011	9.9 (5.0-44.1)	5.6 (3.0-21.5)	0.021	9.0 (5.3-15.2)	5.6 (3.2-28.1)	0.18
Diagnostic group			1.00			0.62			0.84
Medical	25 (25%)	28 (25%)		13 (18%)	12 (17%)		4 (14%)	3 (18%)	
Surgical cardiac	34 (35%)	39 (35%)		23 (31%)	18 (25%)		3 (11%)	1 (6%)	
Surgical other	39 (40%)	44 (40%)		37 (51%)	42 (58%)		21 (75%)	13 (76%)	
Mechanical ventilation on admission	95 (97%)	102 (92%)	0.14	70 (96%)	65 (90%)	0.21	28 (100%)	15 (88%)	0.14
Haemodynamic support on admission	52 (53%)	54 (49%)	0.58	40 (55%)	32 (44%)	0.25	15 (54%)	6 (35%)	0.56

Data are n (%), median (IQR), or mean (SD). PELOD = Paediatric Logistic Organ Dysfunction, range 0-71, with higher scores indicating more severe illness, PIM2 = Paediatric Index of Mortality 2, higher score reflecting a higher risk of mortality, PN=parenteral nutrition.

[a] Proportions: Chi square test (Fisher's exact test if necessary), means: independent t-test, medians: Mann-Whitney U test.

[b] Neonates <1 week: birthweight-for-gestational age Z-score,[130] neonates ≥1 week: weight-for-age Z-score.[131]

[c] Based on PIM2 score =([exp (PIM2)]/[1+exp (PIM2)])*100%.

In neonates younger than 1 day, the PELOD scores were significantly higher in the Early-PN group than in the Late-PN group (Table 1), which also contained a higher proportion of patients with congenital diaphragmatic hernia and a lower proportion of patients with gastroschisis than the late parenteral nutrition group (Appendix). In the subgroup of neonates without enteral nutrition, baseline characteristics were similar, but with similar disproportionate distribution of diagnoses (Appendix).

In univariable analysis, late parenteral nutrition reduced the risk of acquiring a new infection in all age groups (Tables 2, 3, 4). In multivariable analysis, this effect of Late-PN was only maintained in neonates aged up to and including 1 week and younger than 1 day (Tables 2, 3, 4). Statistical power (one-tailed test, α 0.05) retrospectively calculated for the observed differences in risk of new infection in univariable analysis was 79.6%, 92.3%, and 95.4% for neonates aged up to and including 4 weeks and aged up to and including 1 week, and younger than 1 day, respectively. Starting from the observed risk of new infection in the Early-PN, the minimally demonstrable risk reduction versus the observed absolute risk reduction (one-tailed) with Late-PN for new infections in the paediatric ICU, accepting an α of 0.05 and a power of 80%, was -14.5% versus -14.4% in neonates aged up to and including 4 weeks,-18.1% versus -21.7% in those aged up to and including 1 week, and -36.5% versus -45.3% in those younger than 1 day. Late-PN also shortened the duration of paediatric ICU dependency, with a higher likelihood of an earlier live discharge at any time in neonates aged up to and including 4 weeks and aged up to and including 1 week (Tables 2, 3). Further adjustments for age in neonates aged up to and including 4 weeks did not affect the main outcomes (Appendix).

Mortality was similar for Late-PN versus Early-PN in all age groups (Tables 2, 3, 4). The risk of having an episode of hypoglycaemia was significantly higher with Late-PN versus Early-PN for neonates aged up to and including 4 weeks and those aged up to and including 1 week (Tables 2, 3). Further adjustment for age in neonates aged up to and including 4 weeks did not affect the safety outcomes (Appendix). 83 hypoglycaemic episodes were further analysed (Appendix). This analysis showed that none of the episodes was symptomatic, and 94% occurred during insulin administration. Time to recovery from hypoglycaemia was equally fast in both treatment groups after a median of approximately 58 min, and in 84% of the cases at the first glucose check. However, this outcome could be analysed only in neonates in Belgium (n=60) because the exact time of glucose measurements had not been recorded by bedside glucometers used in other centres.

In all age groups, the need for mechanical ventilation was shorter with Late-PN, with a higher likelihood of being weaned alive from the ventilator at any time, than with Early-PN (Tables 2, 3, 4). In neonates aged up to and including 4 weeks and aged up to and including 1 week, plasma urea concentrations and direct health-care costs were lower in the Late-PN group compared with the Early-PN (Tables 2, 3).

Table 2: Outcomes for neonates aged ≤4 weeks

	Early-PN (n=98)	Late-PN (n=111)	Univariable OR, HR or β (95% CI)	P-value[a]	OR, HR or β, adjusted for baseline risk factors[b] (95% CI)	P-value[b]
Efficacy endpoint						
PICU-acquired infections	30 (31%)	18 (16%)	0.44 (0.22-0.85)	0.020	0.54 (0.27-1.08)	0.082
Airway	9 (9%)	6 (5%)		0.42		
Bloodstream	8 (8%)	2 (2%)		0.048		
Urinary tract	3 (3%)	1 (1%)		0.34		
Central nerve system	1 (1%)	0 (0%)		0.47		
Soft Tissue	2 (2%)	2 (2%)		1.00		
Others	0 (0%)	1 (1%)		1.00		
Duration of PICU dependency (days)	7 (3.75-15.75)	5 (3-9)	1.71 (127-2.30)	0.0066	1.61 (1.19-2.20)	0.0021
Duration of mechanical ventilatory support (days)	5 (3-13)	3 (2-6)	1.69 (1.26-2.27)	0.0021	1.62 (1.19-2.21)	0.0020
Highest plasma level of urea (mg/dl)	43 (32-56.75)	33 (20.25-43)	-15.7 (-22.3;-9.10)	<0.0001	-13.4 (-19.6;-7.1)	<0.0001
Duration of hospital stay (days)	18 (9-32.3)	14 (9-29)	1.47 (1.09-1.99)	0.43	1.38 (1.02-1.88)	0.037
Direct healthcare costs (€)[c]	62.260 (110.820)	36.380 (39.100)	-25.880 (-48.110; -3.640)	0.030	-22.971 (-45.603;-339)	0.047
Safety endpoint						
Death during first week	6 (6%)	2 (2%)	0.28 (0.06-1.43	0.15	0.71 (0.09-5.61)	0.74
90-day mortality[d]	15 (15%)	6 (5%)	0.32 (0.12-0.85)	0.018	0.41 (0.13-1.30)	0.13
Hypoglycaemia (blood glucose <40 mg/dl [<2.2 mmol/l]) during first week	14 (14%)	26 (23%)	1.84 (0.90-3.76)	0.11	3.05 (1.27-7.35)	0.013

Data are n (%), median (IQR), or mean (SD). HR = hazard ratio, OR = odds ratio, PELOD = Paediatric Logistic Organ Dysfunction, PICU = paediatric intensive care unit, PIM2 = Paediatric Index of Mortality 2, PN = parenteral nutrition.

[a] Proportions: Fisher's exact test, means: independent t-test, medians: Mann-Whitney U test.

[b] Baseline risk factors: centre, diagnosis group, PELOD, PIM2, weight-for-age z-score; OR and HR are shown for Late-PN versus Early-PN.

[c] Only of Dutch and Belgian patients (Early-PN n=98, Late-PN n=110).

[d] All non-surviving patients died in PICU, hence PICU mortality and hospital mortality were exactly the same as 90-day mortality.

Table 3: Outcomes for neonates aged ≤1 week

	Early-PN (n=73)	Late-PN (n=72)	Univariable OR, HR or β (95% CI)	P-value[a]	OR, HR or β, adjusted for baseline risk factors[b] (95% CI)	P-value[b]
Efficacy endpoint						
PICU-acquired infections	26 (36%)	10 (14%)	0.29 (0.13-0.66)	0.0036	0.36 (0.15-0.83)	0.017
Airway	8 (11%)	5 (7%)		0.56		
Bloodstream	7 (10%)	1 (1%)		0.063		
Urinary tract	2 (3%)	0 (0%)		0.50		
Central nerve system	1 (1%)	0 (0%)		1.00		
Soft Tissue	2 (3%)	1 (1%)		1.00		
Others	0 (0%)	1 (1%)		0.50		
Duration of PICU dependency (days)	7 (3.5-19)	5 (3-9)	1.87 (1.31-2.67)	0.016	1.69 (1.16-2.46)	0.0063
Duration of mechanical ventilatory support (days)	4 (3-14)	3 (2-6)	1.78 (1.25-2.54)	0.015	1.61 (1.10-2.35)	0.014
Highest plasma level of urea (mg/dl)	43 (32-59)	33 (21.5-44)	-18.6 (-26.9;-10.2)	<0.0001	-15.1 (-22.9;-7.3)	0.00020
Duration of hospital stay (days)	21 (10-37)	18.5 (11-35.5)	1.45 (1.01-2.01)	0.99	1.29 (0.88-1.88)	0.19
Direct healthcare costs (€)	67.000 (111.720)	37.760 (30.430)	-29.250 (-56.210; -2.280)	0.034	-29.760 (-58.200;-1.320)	0.040
Safety endpoint						
Death during first week	6 (8%)	1 (1%)	0.16 (0.02-1.34)	0.12	0.47 (0.04-5.83)	0.56
90-day mortality[c]	12 (16%)	3 (4%)	0.22 (0.06-0.82)	0.026	0.31 (0.07-1.44)	0.13
Hypoglycaemia (blood glucose <40 mg/dl [<2.2 mmol/l]) during first week after randomisation	10 (14%)	17 (24%)	1.95 (0.82-4.61)	0.14	3.57 (1.23-10.45)	0.019

Data are n (%), median (IQR), or mean (SD). HR = hazard ratio, OR = odds ratio, PICU = paediatric intensive care unit, PN = parenteral nutrition.

[a] Proportions: Fisher's exact test, means: independent t-test, medians: Mann-Whitney U test.

[b] Baseline risk factors: centre, diagnosis group, PELOD, PIM2, weight-for-age z-score; OR and HR are shown for Late-PN versus Early-PN.

[c] All non-surviving patients died in PICU, hence PICU mortality and hospital mortality were exactly the same as 90-day mortality.

Table 4: Most important outcomes for neonates aged <1 day

Endpoint	Early-PN (n=28)	Late-PN (n=17)	Univariable HR or OR (95% CI)	P-value[a]	HR or OR, adjusted for baseline risk factors[b] (95% CI)	P-value[b]
PICU-acquired infections	16 (57%)	2 (12%)	0.10 (0.02-0.52)	0.0041	0.10 (0.01-0.64)	0.015
Duration of PICU dependency (days)	15 (7.5-35.75)	6 (4-14.5)	2.11 (1.09-4.09)	0.036	1.95 (0.93-4.12)	0.078
Duration of mechanical ventilatory support (days)	12 (5.75-31)	4 (2-12.5)	2.24 (1.16-4.32)	0.0086	2.63 (1.23-5.63)	0.013
90-day mortality	4 (14%)	1 (6%)	0.38 (0.04-3.67)	0.64		
Hypoglycaemia (blood glucose <40 mg/dl [<2.2 mmol/l]) during first week after randomisation	2 (7%)	2 (12%)	1.73 (0.22-13.61)	0.63		

Data are n (%), median (IQR), or mean (SD). HR = hazard ratio, OR = odds ratio, PICU = paediatric intensive care unit, PN = parenteral nutrition.

[a] Proportions: Fisher's exact test, means: independent t-test, medians: Mann-Whitney U test.

[b] Adjusted for centre, diagnosis group, PELOD, PIM2, weight-for-age z-score; OR and HR are shown for Late-PN versus Early-PN.

38 neonates (18%) who stayed in the paediatric ICU for at least 7 days had received no or minimal EN during the first week. This group consisted predominantly of neonates aged up to and including 1 week (n=33, 87%) and the most prominent diagnosis groups were abdominal surgery (n=20, 53%), and cardiac surgery (n=15, 40%). The proportion of patients who received no or minimal EN because of a contraindication (defined as EN being prohibited during at least 3 days) was 61% in the Early-PN group versus 47% in the Late-PN group (p=0.39). The main outcomes among neonates without enteral intake differed from the entire group of neonates with a high incidence of new infections, longer stay in the PICU, longer dependency on mechanical ventilation, and a higher 90-day mortality. Given the severity of illness scores and risk of mortality on admission for neonates who received no EN, these participants should be considered as more severely ill (Table 5 and Appendix). In this group of neonates, withholding PN increased the likelihood of earlier live weaning from mechanical ventilation and increased the risk of hypoglycaemia. The effect of Late-PN versus Early-PN on other main outcomes in neonates without enteral intake followed the same direction as in the total group of neonates, but the analysis was low in power because of the small sample size (Table 5).

Table 5: Most important outcomes for neonates who received no or minimal EN

Endpoint	Early-PN (n=23)	Late-PN (n=15)	Univariable HR or OR (95% CI)	P-value[a]	HR or OR, adjusted for baseline risk factors[b] (95% CI)	P-value[b]
PICU-acquired infections	16 (70%)	7 (47%)	0.38 (0.10-1.47)	0.19	0.57 (0.10-3.41)	0.54
Duration of PICU dependency (days)	19 (13-33)	17 (9-31)	1.58 (0.75-3.34)	0.46	1.83 (0.79-4.24)	0.16
Duration of mechanical ventilatory support (days)	17(9-33)	11 (5-20)	1.83 (0.87-3.86)	0.068	2.55 (1.09-5.96)	0.031
90-day mortality	7 (30%)	2 (13%)	0.35 (0.06-1.99)	0.23		
Hypoglycaemia (blood glucose <40 mg/dl [<2.2 mmol/l]) during first week after randomisation	4 (17%)	8 (53%)	5.43 (1.24-23.86)	0.033		

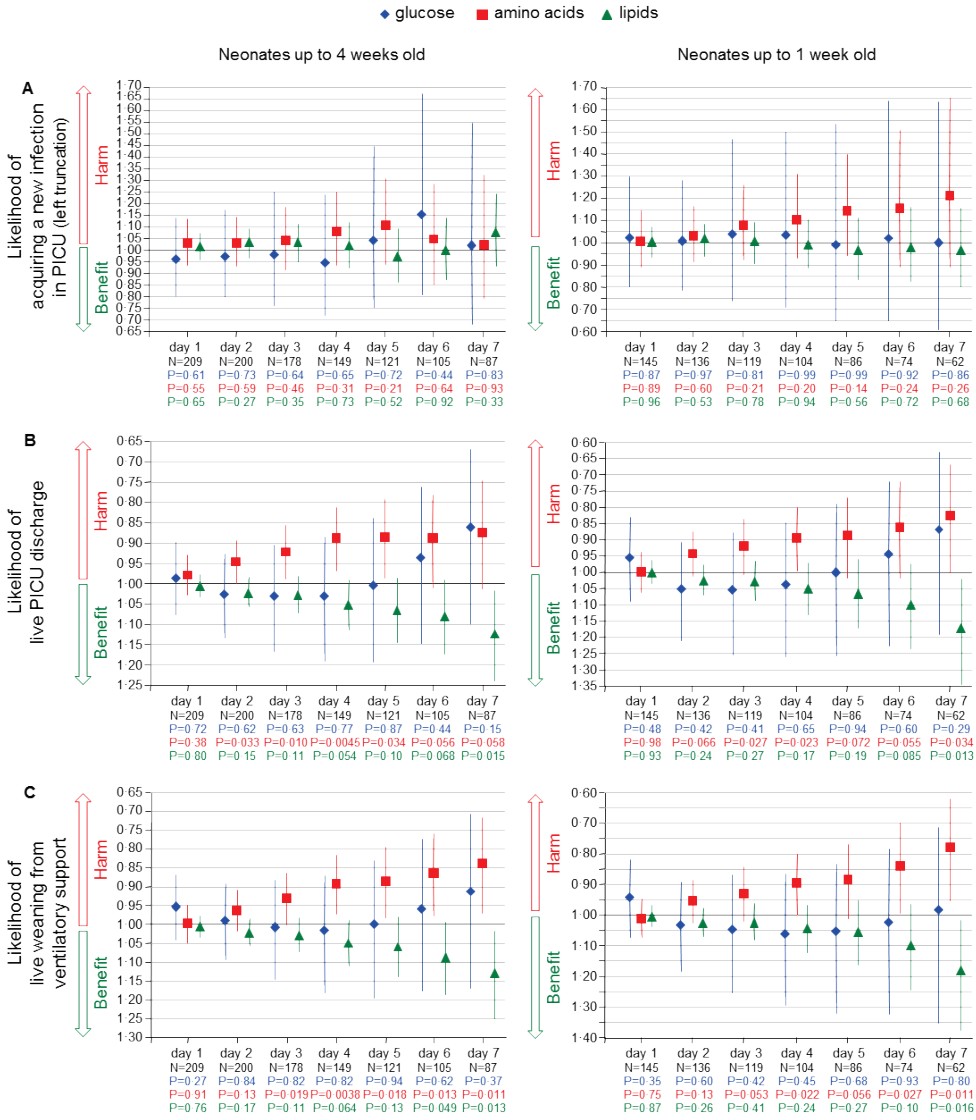
Data are n (%), median (IQR), or mean (SD). EN = enteral nutrition, HR = hazard ratio, OR = odds ratio, PICU = paediatric intensive care unit, PN = parenteral nutrition.

[a] Proportions: Fisher's exact test , means: independent t-test, medians: Mann-Whitney U test.

[b] Adjusted for centre, diagnosis group, PELOD, PIM2, weight-for-age z-score, OR and HR are shown for Late-PN versus Early-PN.

The multivariable models showed no association of average doses of any of the individual macronutrients with the likelihood of acquiring a new infection (Figure 1). In neonates aged up to and including 4 weeks, higher average doses of amino acids were associated with a lower likelihood of earlier live discharge from the paediatric ICU from day 2 to day 5 (HR 0.56–0.71, p≤0.04). In neonates aged up to and including 1 week, a similar association reached significance for doses up to days 3, 4, and 7 (HR 0.42–0.70, p≤0.04; Figure 1). Higher average doses of amino acids were also associated with a lower likelihood of earlier live weaning from mechanical ventilation from day 3 onwards in neonates aged up to and including 4 weeks (HR 0.44–0.66, p≤0.01; Figure 1). A similar association with amino acids occurred in neonates aged up to and including 1 week, with significance reached for average doses administered up to days 4, 6, and 7 (HR 0.32–0.58, p≤0.03; Figure 1). No association occurred between the average doses of glucose and any of the efficacy endpoints. Higher average doses of lipids were associated with a higher likelihood of an earlier live discharge at day 7 in both neonates aged up to and including 4 weeks (HR 1.66, 95% CI 1.11–2.52; p=0.015) and aged up to and including 1 week (2.00, 1.15–3.45; p=0.013). Higher average doses of lipids were also associated with a higher likelihood of an earlier live weaning from mechanical ventilation in neonates aged up to and including 4 weeks (up to days 6 and 7, HR 1.46–1.73; p<0.05) and those aged up to and including 1 week (up to day 7, HR 2.10, 95% CI 1.17–3.93, p=0.016; Figure 1).

Figure 1: Association of average total macronutrient doses in each of the first 7 days in paediatric intensive care unit with clinical outcomes



Data are hazard ratios (HR; 95% Cis) per g macronutrient/kg added. The figure shows associations of average daily doses of the individual macronutrients up to each of the 7 days with the likelihood of (A) acquiring a new infection in the PICU, (B) earlier live PICU discharge, and (C) earlier live weaning from mechanical ventilation. Results were obtained after adjustment for centre, Paediatric Logistic Organ Dysfunction (PELOD) score, Paediatric Index of Mortality 2 (PIM2) score, diagnosis group and weight-for-age Z-scores on admission. A HR >1 indicates a higher likelihood of acquiring a new infection (indicating harm), but a higher likelihood of live weaning from mechanical ventilation and of live PICU discharge (indicating benefit), and vice versa for a HR <1. N represents the number of patients still in the PICU on the day of analysis. The dotted lines represent a neutral relationship in form of HRs being equal to 1 (border between harm and benefit).

PICU = paediatric intensive care unit.

DISCUSSION

Withholding supplemental PN for 1 week in critically ill, term neonates admitted to a paediatric ICU was superior to Early-PN given within 24 hours from a clinical and health-economical perspective. Late-PN resulted in fewer nosocomial infections in neonates aged up to and including 1 week and younger than 1 day, and in a shorter dependency on intensive care and mechanical ventilation for all studied age groups of neonates. The benefits of Late-PN were noted irrespective of centre, disease severity, risk of mortality, diagnosis and nutritional status upon admission. In neonates younger than 1 day, the benefits and large treatment effects observed should be interpreted with the small sample size and differences in diagnoses in consideration, although the direction of the effect was also consistently in favour of Late-PN.

Taking statistical power into consideration, the benefits of withholding PN during critical illness occurred for term neonates in agreement with findings for older children and adults.[18,123] This observation contrasted with concerns that have been raised by experts that neonates are more susceptible to macronutrient deficits.[71-73] A pathophysiological explanation would help to support the clinical findings and abate remaining concerns. Underlying mechanisms of the clinical benefits of withholding PN cannot be determined by our study and remain speculative. However, a role for better activation of autophagy - a process essential for innate immunity, cellular damage control and preservation of endogenous energy supply during critical illness - seems plausible.[132,133] Whereas autophagy is activated during fasting, both during the physiological transition from foetal to neonatal life as well as during critical illness-related anorexia, it is inhibited with Early-PN.[132,133] Furthermore, production of ketone bodies as fuel for the brain is facilitated in foetuses by brown adipose tissue.[134] Thus, efficient ketone body production and upregulated autophagy could provide strategies to manage a macronutrient deficit during acute critical illness in the neonatal period. Such resilience to a macronutrient deficit might also account for why the results in the group of critically ill, term neonates incapable of receiving any EN during the first week seemed to achieve similar benefits as noted with Late-PN in the whole group of neonates. However, the small number of patients did not allow us to draw any firm conclusions.

Safety aspects of Late-PN need to be considered. We showed that, although Late-PN did not affect mortality, it did increase the incidence of hypoglycaemia, which necessitates caution when applied to this vulnerable patient group. Neonates receiving no or minimal EN had the highest risk for developing hypoglycaemia. Increased monitoring of neonates when PN is withheld, especially neonates with no or minimal EN and those who are receiving insulin, remains warranted. Symptomatic, prolonged and recurrent hypoglycaemia might cause serious short-term harmful effects in neonates.[135] However, long-term consequences of brief episodes of asymptomatic hypoglycaemia reported in previous studies in preterm neonates and healthy newborn babies are contradictory and remain a subject of debate.[19,21-23] Critically ill infants and children examined 4 years after a large study of glycaemic control did not show

negative effects of hypoglycaemia on neurocognitive functioning.[20] However, real-time continuous glucose monitoring was unavailable in all centres and thus unnoticed hypoglycaemic periods up to 1 hour cannot be excluded. Whether the hypoglycaemic incidents in our Late-PN group affected long-term neurocognitive outcome is yet to be established. A long-term follow-up of the patients is currently ongoing.

In line with a secondary analysis of all children included in the PEPaNIC trial,[70] we showed in a similar explanatory analysis that higher amounts of amino acids, rather than glucose or lipids, were associated with prolonged need for mechanical ventilation and intensive care in critically ill term neonates, a population that required mechanical ventilation and intensive care for a longer time than the older patients in the PEPaNIC trial. Current advice for amino acid intake is based on studies investigating nitrogen balance as outcome measure.[74,136] Based on exclusively preterm neonatal research, amino acid intake in neonates is advised to be started as soon as possible after birth to avoid the metabolic derangement caused by the interruption of continuous feeding that is present in utero.[137] Higher amounts of amino acids indeed result in positive nitrogen balances and an anabolic state, though at the cost of higher urea concentrations and higher amino acid oxidation rates.[3,138,139] Furthermore, no long-term beneficial effects of early high amino acid administration were noted.[140] Thus, the optimum amount of amino acid administration in preterm neonates is under debate.[140] Although findings in preterm neonates cannot be extrapolated to term neonates, they raise questions about the presumed beneficial effect of early high amounts of amino acids in critically ill, term neonates. In that regard, our present data call for caution, as higher amino acid doses appeared to be associated with delayed recovery and with higher plasma urea concentrations, highlighting the need for addressing causality in an adequately powered randomised trial.

One strength of our study was the randomised design in a large group of critically ill neonates. Another asset is the clinically relevant outcome measures, unique for nutritional studies in this population. Important limitations are the insufficient power in some of the sub-analyses, and the observational design of the explanatory macronutrient dose analyses. Another major limitation was that the baseline characteristics differed between the randomisation groups. However, we corrected for this during the multivariable analyses. A final limitation is the absence of data on (long-term) growth.

CONCLUSIONS

Withholding PN for 1 week during critical illness in term neonates, while administering micronutrients during this time, is superior to early initiation of PN from a short-term clinical and health-economical perspective. However, withholding PN for 1 week significantly increased the risk of developing hypoglycaemia, necessitating frequent monitoring of blood glucose concentrations. Long-term effects of hypoglycaemia need to be investigated before Late-PN can be confidently recommended for this vulnerable patient group.

APPENDIX

Methods S1: Protocol for scoring of infections

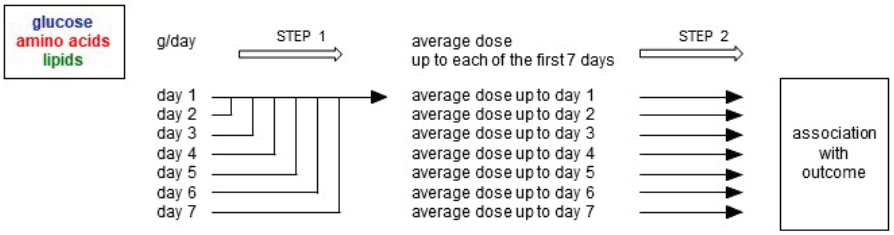
Data export

All patients receiving antimicrobial agents were identified by the data manager, who provided an export of all patient numbers with all the information on antimicrobial agents given as well as the duration of such treatment.

Identification of patients with infections

The infectious disease specialists, who were blinded for treatment allocation, selected all patients receiving antimicrobial agents for more than 48 hours, after excluding all patients who received prophylaxis. Each patient who fulfilled the criteria for infection, as well as the type of infection, was identified as such based on thorough review of the medical record. Patients for whom antimicrobials where initiated prior to paediatric ICU admission or within the first 48 hours of admission while the criteria for infection were fulfilled, were labelled as "having an infection upon admission". When antimicrobial agents were initiated after randomization and beyond the first 48 hours in the paediatric ICU, and were given for more than 48 hours while the criteria for infection were fulfilled, the patient was labelled as "having a new infection".[18]

Methods S2: Stepwise transformation of the given doses of glucose, lipid, and amino acids and association with clinical outcomes

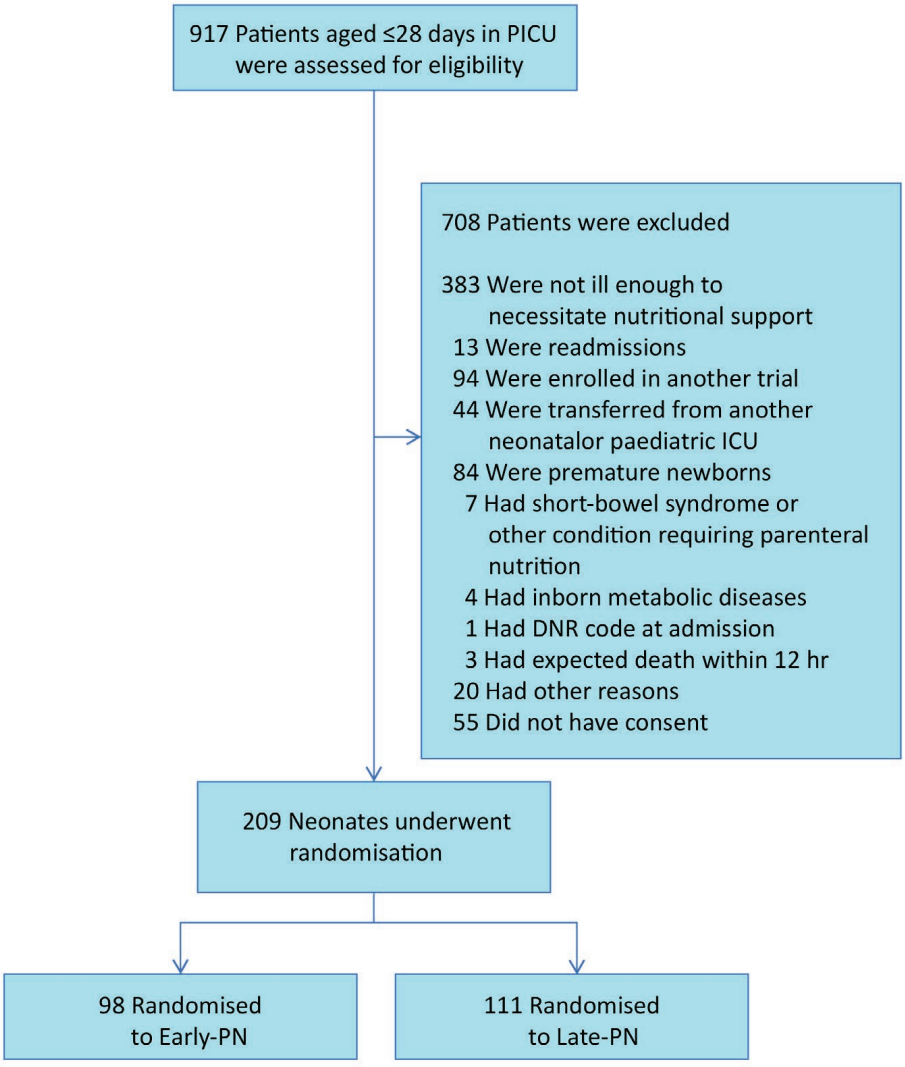


In a first step, doses of glucose, lipid, and amino acids as the crude grams per kilogram per day that were given on each of the first 7 days in paediatric ICU were used to calculate average doses of glucose, lipid, and amino acids administered up to each of the first 7 days in paediatric ICU for all patients who were still in paediatric ICU on these respective days.

In a second step, associations of these average doses up to each of the first 7 days in paediatric ICU with the clinical endpoints (time to the first new infection acquired in the paediatric ICU, the time to live discharge from paediatric ICU accounting for mortality as a competing risk, and the time to live weaning from mechanical ventilatory support) were determined with Cox proportional hazard analyses, adjusting for centre, Paediatric Logistic Organ Dysfunction (PELOD) score, Paediatric Index of Mortality 2 (PIM2) score, diagnosis group and weight-for-age Z-scores on admission.

This procedure was performed for total doses and repeated for enteral doses and parenteral doses of glucose, lipid, and amino acids.

Figure S1: Consort flow diagram



DNR = do not resuscitate, ICU = intensive care unit, PICU = paediatric intensive care unit.

Table S1A: Average macronutrient administration for up to each of the first 7 days in paediatric ICU to neonates aged ≤4 weeks

			Glucose		Amino acids		Lipids	
Route	**Dose up to day**	**n**	**Early-PN**	**Late-PN**	**Early-PN**	**Late-PN**	**Early-PN**	**Late-PN**
Total dose	1	209	4.64 (2.73-7.10)	1.71 (1.29-2.72)	1.14 (0.00-1.57)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
(g/kg)	2	200	6.44 (4.63-8.87)	2.34 (1.94-3.86)	1.64 (0.98-2.04)	0.00 (0.00-0.18)	0.71 (0.09-1.20)	0.00 (0.00-0.31)
	3	178	7.14 (5.40-9.71)	2.88 (2.22-4.42)	1.77 (1.37-2.15)	0.04 (0.00-0.42)	1.34 (0.60-2.08)	0.12 (0.00-0.80)
	4	149	7.82 (5.50-10.71)	3.27 (2.42-4.84)	1.91 (1.63-2.15)	0.06 (0.00-0.50)	1.81 (1.19-2.59)	0.13 (0.00-1.29)
	5	121	8.16 (5.93-11.27)	3.78 (2.65-5.30)	1.97 (1.76-2.16)	0.10 (0.00-0.54)	2.31 (1.59-2.94)	0.26 (0.00-1.37)
	6	105	8.50 (6.11-11.33)	4.04 (3.03-6.30)	2.01 (1.80-2.21)	0.16 (0.02-0.77)	2.63 (1.90-3.11)	0.40 (0.05-1.78)
	7	87	8.56 (6.45-11.33)	4.37 (3.29-6.00)	1.99 (1.85-2.26)	0.24 (0.04-0.71)	2.84 (2.05-3.41)	0.71 (0.09-1.45)
Enteral dose	1	209	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
(g/kg)	2	200	0.00 (0.00-0.00)	0.00 (0.00-0.44)	0.00 (0.00-0.00)	0.00 (0.00-0.07)	0.00 (0.00-0.00)	0.00 (0.00-0.22)
	3	178	0.00 (0.00-0.61)	0.17 (0.00-1.65)	0.00 (0.00-0.10)	0.03 (0.00-0.28)	0.00 (0.00-0.34)	0.08 (0.00-0.78)
	4	149	0.11 (0.00-1.60)	0.21 (0.00-2.41)	0.01 (0.00-0.30)	0.03 (0.00-0.38)	0.04 (0.00-0.71)	0.11 (0.00-1.28)
	5	121	0.30 (0.00-2.13)	0.48 (0.00-2.66)	0.05 (0.00-0.33)	0.09 (0.00-0.47)	0.15 (0.00-1.06)	0.23 (0.00-1.37)
	6	105	0.45 (0.00-2.07)	0.75 (0.10-3.57)	0.08 (0.00-0.41)	0.13 (0.02-0.61)	0.22 (0.00-1.02)	0.39 (0.05-1.78)
	7	87	0.37 (0.00-2.99)	1.28 (0.03-2.86)	0.06 (0.00-0.56)	0.23 (0.01-0.49)	0.21 (0.00-1.36)	0.71 (0.02-1.45)
Parenteral dose	1	209	4.58 (2.68-7.03)	1.70 (1.22-2.58)	1.11 (0.00-1.57)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
(g/kg)	2	200	5.97 (4.08-8.45)	2.09 (1.63-2.83)	1.60 (0.87-2.02)	0.00 (0.00-0.00)	0.52 (0.00-0.94)	0.00 (0.00-0.00)
	3	178	6.22 (4.21-9.04)	2.14 (1.67-2.94)	1.65 (1.28-2.10)	0.00 (0.00-0.00)	0.97 (0.27-1.78)	0.00 (0.00-0.00)
	4	149	5.82 (3.99-10.08)	2.33 (1.74-3.14)	1.78 (1.25-2.05)	0.00 (0.00-0.00)	1.25 (0.49-2.13)	0.00 (0.00-0.00)
	5	121	6.09 (4.13-10.13)	2.36 (1.95-3.24)	1.83 (1.41-2.06)	0.00 (0.00-0.00)	1.64 (0.85-2.46)	0.00 (0.00-0.00)
	6	105	6.34 (3.95-10.44)	2.41 (1.92-3.43)	1.85 (1.42-2.06)	0.00 (0.00-0.00)	1.85 (0.91-2.53)	0.00 (0.00-0.00)
	7	87	6.52 (3.66-10.33)	2.45 (1.89-3.57)	1.88 (1.15-2.04)	0.00 (0.00-0.03)	1.91 (0.86-2.73)	0.00 (0.00-0.01)

Data represent medians and interquartile ranges. All total doses and parenteral doses, but not enteral doses (except on day 2), of glucose, amino acids, and lipids were significantly different for patients in the Early-PN and Late-PN groups. N indicates the number of patients still in paediatric ICU on the day of analysis.

ICU = intensive care unit, PN = parenteral nutrition.

Table S1b: Average macronutrient administration for up to each of the first 7 days in paediatric ICU to neonates aged ≤1 week

			Glucose		Amino acids		Lipids	
Route	**Dose up to day**	**n**	**Early-PN**	**Late-PN**	**Early-PN**	**Late-PN**	**Early-PN**	**Late-PN**
Total dose	1	145	4.55 (2.72-6.88)	1.71 (1.17-2.41)	1.23 (0.00-1.60)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
(g/kg)	2	136	5.98 (4.31-8.37)	2.27 (1.90-3.20)	1.76 (0.97-2.04)	0.00 (0.00-0.07)	0.67 (0.09-1.00)	0.00 (0.00-0.09)
	3	119	6.76 (4.89-9.14)	2.53 (2.12-3.61)	1.85 (1.36-2.13)	0.00 (0.00-0.09)	1.26 (0.60-2.01)	0.00 (0.00-0.15)
	4	104	6.80 (5.06-10.57)	2.98 (2.34-3.85)	1.92 (1.63-2.15)	0.00 (0.00-0.11)	1.71 (1.20-2.52)	0.00 (0.00-0.26)
	5	86	7.03 (5.57-10.24)	3.41 (2.56-4.13)	1.95 (1.76-2.15)	0.03 (0.00-0.15)	2.29 (1.65-2.87)	0.09 (0.00-0.40)
	6	74	7.44 (5.73-10.87)	3.77 (2.82-4.52)	1.98 (1.80-2.20)	0.05 (0.00-0.23)	2.66 (1.91-3.11)	0.16 (0.00-0.58)
	7	62	7.79 (6.30-10.88)	4.24 (2.82-4.90)	1.98 (1.86-2.21)	0.12 (0.03-0.40)	2.87 (2.08-3.35)	0.15 (0.04-0.89)
Enteral dose	1	145	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
(g/kg)	2	136	0.00 (0.00-0.00)	0.00 (0.00-0.15)	0.00 (0.00-0.00)	0.00 (0.00-0.02)	0.00 (0.00-0.00)	0.00 (0.00-0.07)
	3	119	0.00 (0.00-0.23)	0.00 (0.00-0.25)	0.00 (0.00-0.04)	0.00 (0.00-0.04)	0.00 (0.00-0.11)	0.00 (0.00-0.13)
	4	104	0.00 (0.00-0.58)	0.00 (0.00-0.44)	0.00 (0.00-0.09)	0.00 (0.00-0.06)	0.00 (0.00-0.28)	0.00 (0.00-0.23)
	5	86	0.13 (0.00-0.86)	0.15 (0.00-0.71)	0.02 (0.00-0.14)	0.02 (0.00-0.11)	0.07 (0.00-0.49)	0.07 (0.00-0.40)
	6	74	0.21 (0.00-1.49)	0.28 (0.00-1.08)	0.04 (0.00-0.26)	0.04 (0.00-0.20)	0.12 (0.00-0.73)	0.16 (0.00-0.58)
	7	62	0.21 (0.00-1.93)	0.21 (0.03-1.80)	0.04 (0.00-0.36)	0.03 (0.00-0.33)	0.12 (0.00-1.02)	0.11 (0.00-0.89)
Parenteral dose	1	145	4.54 (2.72-6.88)	1.71 (1.13-2.37)	1.23 (0.00-1.60)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
(g/kg)	2	136	5.97 (4.17-8.37)	2.15 (1.78-2.96)	1.76 (0.95-2.03)	0.00 (0.00-0.00)	0.61 (0.00-1.00)	0.00 (0.00-0.00)
	3	119	6.40 (4.24-9.04)	2.28 (1.96-3.02)	1.76 (1.34-2.11)	0.00 (0.00-0.00)	1.09 (0.55-1.94)	0.00 (0.00-0.00)
	4	104	6.61 (4.50-10.38)	2.46 (2.08-3.20)	1.83 (1.58-2.05)	0.00 (0.00-0.00)	1.48 (0.86-2.32)	0.00 (0.00-0.00)
	5	86	6.17 (4.60-9.83)	2.56 (2.12-3.37)	1.88 (1.67-2.06)	0.00 (0.00-0.00)	1.81 (1.29-2.56)	0.00 (0.00-0.00)
	6	74	6.34 (4.30-10.36)	2.62 (2.19-3.73)	1.89 (1.68-2.05)	0.00 (0.00-0.00)	1.96 (1.09-2.66)	0.00 (0.00-0.00)
	7	62	6.52 (4.46-9.79)	2.76 (2.31-3.79)	1.90 (1.61-2.06)	0.00 (0.00-0.04)	2.07 (1.39-2.93)	0.00 (0.00-0.04)

Data represent medians and interquartile ranges. All total doses and parenteral doses, but not enteral doses, of glucose, amino acids, and lipids were significantly different for patients in the Early-PN and Late-PN groups, except for the lipid dose on day 1. N indicates the number of patients still in paediatric ICU on the day of analysis.
ICU = intensive care unit, PN = parenteral nutrition.

Table S1c: Average macronutrient administration for up to each of the first 7 days in paediatric ICU to neonates aged <1 day

			Glucose		Amino acids		Lipids	
Route	**Dose up to day**	**n**	**Early-PN**	**Late-PN**	**Early-PN**	**Late-PN**	**Early-PN**	**Late-PN**
Total dose	1	45	3.16 (2.07-4.55)	1.71 (0.81-2.67)	0.00 (0.00-0.51)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
(g/kg)	2	44	4.61 (3.51-5.54)	2.11 (1.82-3.15)	0.88 (0.68-1.22)	0.00 (0.00-0.03)	0.70 (0.46-0.94)	0.00 (0.00-0.05)
	3	41	5.11 (4.20-6.05)	2.39 (2.12-3.53)	1.35 (1.22-1.66)	0.00 (0.00-0.11)	1.55 (0.99-1.99)	0.00 (0.00-0.00)
	4	37	5.52 (4.61-6.61)	2.66 (2.37-3.11)	1.65 (1.50-1.91)	0.00 (0.00-0.02)	2.03 (1.32-2.51)	0.00 (0.00-0.00)
	5	34	5.91 (4.84-7.05)	3.07 (2.44-3.92)	1.87 (1.67-1.96)	0.00 (0.00-0.08)	2.58 (1.92-2.81)	0.00 (0.00-0.04)
	6	32	6.34 (5.22-7.63)	3.46 (2.76-4.63)	1.94 (1.78-2.07)	0.02 (0.00-0.24)	2.68 (2.06-2.98)	0.04 (0.00-0.63)
	7	30	6.86 (5.73-8.13)	4.00 (2.83-5.49)	1.97 (1.90-2.18)	0.04 (0.00-0.68)	2.93 (2.18-3.26)	0.07 (0.00-1.79)
Enteral dose	1	45	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
(g/kg)	2	44	0.00 (0.00-0.00)	0.00 (0.00-0.11)	0.00 (0.00-0.00)	0.00 (0.00-0.02)	0.00 (0.00-0.00)	0.00 (0.00-0.05)
	3	41	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	4	37	0.00 (0.00-0.24)	0.00 (0.00-0.00)	0.00 (0.00-0.04)	0.00 (0.00-0.00)	0.00 (0.00-0.12)	0.00 (0.00-0.00)
	5	34	0.00 (0.00-0.26)	0.00 (0.00-0.07)	0.00 (0.00-0.05)	0.00 (0.00-0.01)	0.00 (0.00-0.14)	0.00 (0.00-0.04)
	6	32	0.00 (0.00-0.45)	0.08 (0.00-1.25)	0.00 (0.00-0.08)	0.01 (0.00-0.21)	0.00 (0.00-0.23)	0.04 (0.00-0.63)
	7	30	0.06 (0.00-0.91)	0.00 (0.00-3.65)	0.01 (0.00-0.20)	0.00 (0.00-0.65)	0.04 (0.00-0.42)	0.00 (0.00-1.76)
Parenteral dose	1	45	3.16 (2.07-4.55)	1.71 (0.81-2.48)	0.00 (0.00-0.51)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
(g/kg)	2	44	4.30 (3.48-5.42)	2.00 (1.58-3.11)	0.88 (0.67-1.22)	0.00 (0.00-0.00)	0.65 (0.02-0.90)	0.00 (0.00-0.00)
	3	41	4.82 (4.02-6.05)	2.34 (1.96-3.00)	1.35 (1.21-1.65)	0.00 (0.00-0.00)	1.42 (0.55-1.97)	0.00 (0.00-0.00)
	4	37	4.80 (4.14-6.61)	2.50 (2.08-2.85)	1.65 (1.48-1.83)	0.00 (0.00-0.00)	1.96 (0.82-2.50)	0.00 (0.00-0.00)
	5	34	5.22 (4.14-7.05)	2.56 (2.29-3.15)	1.78 (1.67-1.96)	0.00 (0.00-0.00)	2.33 (0.83-2.80)	0.00 (0.00-0.00)
	6	32	5.63 (4.21-7.43)	2.69 (2.11-3.57)	1.91 (1.73-2.07)	0.00 (0.00-0.00)	2.48 (0.96-2.91)	0.00 (0.00-0.00)
	7	30	6.26 (4.94-7.87)	2.78 (1.89-4.19)	1.95 (1.83-2.16)	0.00 (0.00-0.04)	2.43 (0.96-3.10)	0.00 (0.00-0.00)

Data represent medians and interquartile ranges. All total doses and parenteral doses, but not enteral doses, of glucose, amino acids, and lipids were significantly different for patients in the Early-PN and Late-PN groups, except for the protein and lipid dose on day 1. N indicates the number of patients still in paediatric ICU on the day of analysis. ICU = intensive care unit, PN = parenteral nutrition.

Table S2: Diagnoses of neonates aged <1 day

Diagnosis	Early-PN (n=28)	Late-PN (n=17)	P-value
Surgical			
Abdominal / Thoracic surgery			
Congenital Diaphragmatic Hernia	17 (61%)	5 (29%)	0.041
Gastroschisis	3 (11%)	6 (35%)	0.045
Other	1 (3%)	2 (12%)	0.30
Cardiac surgery	3 (11%)	1 (6%)	0.58
Non-surgical			
Cardiac	3 (11%)	1 (6%)	0.58
Other	1 (3%)	2 (12%)	0.30

PN = parenteral nutrition.

Table S3: Baseline characteristics of neonates needing intensive care for at least 7 days who did not receive enteral nutrition in the first week in paediatric ICU

	Early-PN (n=23)	Late-PN (n=15)	P-value
Male	15 (65%)	19 (67%)	0.93
Age at randomisation (days)	0 (0-5)	1 (0-6)	0.48
Gestational Age (weeks)	38 (38-39)	38 (37-39)	0.54
Birth Weight (gram)	3100 (2777-3500)	3080 (2700-3330)	0.33
Weight z-score[a]	-0.56 (-1.30;0.41)	-0.85 (-1.26-0.01)	0.73
PELOD score	21 (12-32)	22 (12-32)	1.00
PIM2 score	-1.95 (-2.36;-0.00)	-0.77 (-2.90;-0.08)	0.70
Risk of mortality (%)[b]	12.4 (8.6-50.0)	31.6 (5.2-48.0)	0.70
Diagnostic group			0.76
Medical	2 (9%)	1 (7%)	
Surgical cardiac	8 (35%)	7 (47%)	
Surgical other	13 (56%)	7 (47%)	
Mechanical ventilation on admission	23 (100%)	15 (100%)	-
Haemodynamic support on admission	18 (78%)	19 (67%)	0.43

ICU = intensive care unit, PN = parenteral nutrition.

[a] Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

[b] Based on PIM2 score =([exp (PIM2)]/[1+exp (PIM2)])*100%.

Table S4: Outcomes of neonates needing intensive care for at least 7 days who did not receive enteral nutrition in the first week in paediatric ICU

Diagnosis	Early-PN (n=23)	Late-PN (n=15)	P-value
Surgical			
Abdominal / thoracic surgery			
Congenital Diaphragmatic Hernia	12 (52%)	3 (20%)	0.047
Gastroschisis	1 (4%)	3 (20%)	0.12
Other	0 (0%)	1 (7%)	0.21
Cardiac surgery	8 (35%)	7 (47%)	0.46
Non-surgical			
Cardiac	2 (9%)	0 (%)	0.24
Other	0 (0%)	1 (7%)	0.21

ICU = intensive care unit, PN = parenteral nutrition.

Table S5: Outcomes of neonates aged ≤4 weeks, with further adjustment for age

	Early-PN (n=98)	Late-PN (n=111)	Univariable OR, HR or β (95% CI)	P-value[a]	OR, HR or β, adjusted for baseline risk factors (95% CI)[b]	P-value[b]
Efficacy endpoint						
PICU-acquired infections	30 (31%)	18 (16%)	0.44 (0.22-0.85)	0.020	0.55 (0.27-1.10)	0.092
Airway	9 (9%)	6 (5%)		0.42		
Bloodstream	8 (8%)	2 (2%)		0.048		
Urinary tract	3 (3%)	1 (1%)		0.34		
Central nerve system	1 (1%)	0 (0%)		0.47		
Soft Tissue	2 (2%)	2 (1%)		1.00		
Others	0 (0%)	1 (1%)		1.00		
Duration of PICU dependency (days)	7 (3.75-15.75)	5 (3-9)	1.71 (127-2.30)	0.0066	1.59 (1.17-2.16)	0.0031
Duration of mechanical ventilatory support (days)	5 (3-13)	3 (2-6)	1.69 (1.26-2.27)	0.0021	1.60 (1.18-2.18)	0.0027
Highest plasma level of urea (mg/d)	43 (32-57)	33 (20-43)	-15.7 (-22.3;-9.10)	<0.0001	-13.2 (-19.5;-6.9)	<0.0001
Duration of hospital stay (days	18 (9-32)	14 (9-29)	1.47 (1.09-1.99)	0.43	1.33 (0.98-1.82)	0.068
Direct healthcare costs (€)[c]	62.260 (110.820)	36.380 (39.100)	-25.880 (-48.110; -3.640)	0.030	-22.560 (-45.390;260)	0.053
Safety endpoint						
Death during first week)	6 (6%)	2 (2%)	0.28 (0.06-1.43	0.15	0.81 (0.08-7.85)	0.86
90-day mortality)	15 (15%)	6 (5%)	0.32 (0.12-0.85)	0.018	0.40 (0.12-1.28)	0.12
Hypoglycaemia (blood glucose <40 mg/dl [<2.2 mmol/l]) during first week	14 (14%)	26 (23%)	1.84 (0.90-3.76)	0.11	3.32 (1.36-8.08)	0.0082

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2, PICU = paediatric intensive care unit.

[a] Proportions: Chi square test (Fisher's exact test if necessary), means: independent t-test, medians: Mann-Whitney U test.

[b] Baseline risk factors: centre, diagnosis group, PELOD, PIM2, weight-for-age z-score, **and age**; OR and HR are shown for Late-PN versus Early-PN.

[c] Only of Dutch and Belgian patients (Early-PN n=98, Late-PN n=110).

[d] All non-surviving patients died in paediatric ICU, hence PICU mortality and hospital mortality were exactly the same as 90-day mortality.

Table S6: Episodes of hypoglycaemia

	Early-PN (n=35)	Late-PN (n=48)	Univariable P-value
Lowest level of blood glucose – mg/dL	37 (33.3-38)	34.5 (29-37)	0.032
Time-to-recovery from hypoglycaemia[a] – minutes	58 (45-88)	58.5 (48-76)	0.27
Level of blood glucose at recovery– mg/dL	73 (54-94)	58.5 (48-76)	0.065

PN = parenteral nutrition.

[a]Only in Belgian neonates (n=60).

Table S7-1A: Multivariable linear regression analysis determining significant and independent associations between baseline risk factors and acquiring new infections in the neonates aged ≤4 weeks

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.54 (0.27-1.08)	0.082
Centre Rotterdam vs Leuven	2.02 (0.50-8.16)	0.32
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	2.29 (0.66-7.96)	0.19
Diagnosis group Surgical other vs medical	2.19 (0.74-6.50)	0.16
PELOD score (per point added)	1.02 (0.97-1.08)	0.43
PIM2 score (per point added)	1.42 (1.10-1.84)	0.0073
Weight for age Z-score (per Z-score added)[a]	0.94 (0.68-1.29)	0.94

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-1B: Multivariable linear regression analysis determining significant and independent associations between baseline risk factors including age and acquiring new infections in the neonates aged ≤4 weeks

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.55 (0.27-1.10)	0.092
Age (per day added)	0.99 (0.93-1.05)	0.68
Centre Rotterdam vs Leuven	1.91 (0.46-7.97)	0.38
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	2.23 (0.63-7.85)	0.21
Diagnosis group Surgical other vs medical	1.95 (0.58-6.57)	0.28
PELOD score (per point added)	1.02 (0.97-1.08)	0.48
PIM2 score (per point added)	1.41 (1.08-1.83)	0.012
Weight for age Z-score (per Z-score added) [a]	0.92 (0.66-1.29)	0.63

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-2A: Multivariable linear regression analysis determining significant and independent associations between baseline risk factors and time-to-live discharge from the PICU in the neonates aged ≤4 weeks

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1.61 (1.19-2.20)	0.0021
Centre Rotterdam vs Leuven	0.83 (0.45-1.54)	0.56
Centre Edmonton vs Leuven	1.43 (0.19-10.55)	0.73
Diagnosis group Surgery cardiac vs medical	1.29 (0.77-2.16)	0.34
Diagnosis group Surgical other vs medical	1.02 (0.67-1.56)	0.93
PELOD score (per point added)	0.99 (0.96-1.01)	0.24
PIM2 score (per point added)	0.74 (0.65-0.84)	<0.0001
Weight for age Z-score (per Z-score added)[a]	1.06 (0.93-1.22)	0.39

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-2B: Multivariable linear regression analysis determining significant and independent associations between baseline risk factors including age and time-to-live discharge from the PICU in the neonates aged ≤4 weeks

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1.59 (1.17-2.16)	0.0031
Age (per day added)	1.01 (0.99-1.04)	0.30
Centre Rotterdam vs Leuven	0.90 (0.48-1.69)	0.74
Centre Edmonton vs Leuven	1.41 (0.19-10.41)	0.74
Diagnosis group Surgery cardiac vs medical	1.36 (0.80-2.30)	0.26
Diagnosis group Surgical other vs medical	1.17 (0.71-1.94)	0.53
PELOD score (per point added)	0.99 (0.96-1.01)	0.31
PIM2 score (per point added)	0.75 (0.65-0.85)	<0.0001
Weight for age Z-score (per Z-score added) [a]	1.08 (0.94-1.25)	0.28

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-3A: Multivariable linear regression analysis determining significant and independent associations between risk factors and time-to-life weaning from ventilatory support in the neonates aged ≤4 weeks

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1.62 (1.19-2.21)	0.0020
Centre Rotterdam vs Leuven	0.77 (0.41-1.46)	0.42
Centre Edmonton vs Leuven	0.87 (0.12-6.45)	0.89
Diagnosis group Surgery cardiac vs medical	1.17 (0.70-2.00)	0.55
Diagnosis group Surgical other vs medical	1.18 (0.79-1.78)	0.42
PELOD score (per point added)	0.99 (1.00-1.02)	0.60
PIM2 score (per point added)	0.68 (0.59-0.78)	<0.0001
Weight for age Z-score (per Z-score added) [a]	1.06 (0.93-1.22)	0.39

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score
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Table S7-3B: Multivariable linear regression analysis determining significant and independent associations between risk factors including age and time-to-life weaning from ventilatory support in the neonates aged ≤4 weeks

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1.60 (1.18-2.18)	0.0027
Age (per day added)	1.01 (0.98-1.03)	0.71
Centre Rotterdam vs Leuven	0.80 (0.42-1.53)	0.49
Centre Edmonton vs Leuven	0.88 (0.12-6.47)	0.90
Diagnosis group Surgery cardiac vs medical	1.18 (0.70-1.98)	0.54
Diagnosis group Surgical other vs medical	1.22 (0.75-1.98)	0.42
PELOD score (per point added)	0.99 (0.97-1.02)	0.63
PIM2 score (per point added)	0.68 (0.59-0.78)	<0.0001
Weight for age Z-score (per Z-score added)[a]	1.06 (0.93-1.22)	0.39

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-4A: Multivariable linear regression analysis determining significant and independent associations between risk factors and death during the first week in the neonates aged ≤4 weeks

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.71 (0.09-5.61)	0.74
Centre Rotterdam vs Leuven	1.03 (0.05-20.67)	0.99
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	1.51 (0.08-29.14)	0.78
Diagnosis group Surgical other vs medical	1.29 (0.06-29.42)	0.87
PELOD score (per point added)	1.05 (0.94-1.16)	0.42
PIM2 score (per point added)	3.55 (1.59-7.94)	0.0020
Weight for age Z-score (per Z-score added)[a]	1.82 (0.67-4.93)	0.24

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-4B: Multivariable linear regression analysis determining significant and independent associations between risk factors including age and death during the first week in the neonates aged ≤4 weeks

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.81 (0.08-7.85)	0.86
Age (per day added)	0.97 (0.78-1.21)	0.77
Centre Rotterdam vs Leuven	0.72 (0.02-34.75)	0.87
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	1.19 (0.04-34.74)	0.92
Diagnosis group Surgical other vs medical	1.26 (0.06-28.64)	0.89
PELOD score (per point added)	1.05 (0.94-1.17)	0.41
PIM2 score (per point added)	3.57 (1.56-8.15)	0.0025
Weight for age Z-score (per Z-score added)[a]	1.71 (0.58-5.05)	0.33

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-5A: Multivariable linear regression analysis determining significant and independent associations between risk factors and 90 day mortality in the neonates aged ≤4 weeks

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.41 (0.13-1.30)	0.13
Centre Rotterdam vs Leuven	0.83 (0.10-7.08)	0.86
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.59 (0.09-4.01)	0.59
Diagnosis group Surgical other vs medical	0.56 (0.08-3.86)	0.55
PELOD score (per point added)	1.05 (0.98-1.14)	0.17
PIM2 score (per point added)	1.92 (1.33-2.78)	0.00052
Weight for age Z-score (per Z-score added)[a]	1.03 (0.60-1.78)	0.91

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-5B: Multivariable linear regression analysis determining significant and independent associations between risk factors including age and 90 day mortality in the neonates aged ≤4 weeks

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.40 (0.12-1.28)	0.12
Age (per day added)	1.01 (0.92-1.11)	0.78
Centre Rotterdam vs Leuven	0.91 (0.10-8.53)	0.94
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.64 (0.09-4.59)	0.66
Diagnosis group Surgical other vs medical	0.60 (0.08-4.54)	0.62
PELOD score (per point added)	1.05 (0.98-1.14)	0.17
PIM2 score (per point added)	1.95 (1.33-2.86)	0.00064
Weight for age Z-score (per Z-score added)[a]	1.06 (0.60-1.86)	0.85

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-6A: Multivariable linear regression analysis determining significant and independent associations between risk factors and hypoglycaemia in the neonates aged ≤4 weeks

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	3.05 (1.27-7.35)	0.013
Centre Rotterdam vs Leuven	0.12 (0.03-0.59)	0.0087
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.69 (0.17-2.88)	0.61
Diagnosis group Surgical other vs medical	0.96 (0.24-3.87)	0.95
PELOD score (per point added)	1.03 (0.96-1.09)	0.42
PIM2 score (per point added)	1.25 (0.94-1.67)	0.13
Weight for age Z-score (per Z-score added)[a]	0.88 (0.60-1.29)	0.51

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-6B: Multivariable linear regression analysis determining significant and independent associations between risk factors including age and hypoglycaemia in the neonates aged ≤4 weeks

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	3.32 (1.36-8.08)	0.0082
Age (per day added)	0.94 (0.88-1.01)	0.081
Centre Rotterdam vs Leuven	0.09 (0.02-0.46)	0.0042
Centre Edmonton vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.52 (0.11-2.36)	0.39
Diagnosis group Surgical other vs medical	0.54 (0.12-2.52)	0.44
PELOD score (per point added)	1.02 (0.96-1.09)	0.47
PIM2 score (per point added)	1.15 (0.85-1.55)	0.37
Weight for age Z-score (per Z-score added)[a]	0.77 (0.51-1.17)	0.22

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Neonates <1 week: birthweight-for-gestational age Z-score, neonates ≥1 week: weight-for-age Z-score.

Table S7-7: Multivariable linear regression analysis determining significant and independent associations between risk factors and acquiring new infections in the neonates aged ≤1 week

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.36 (0.15-0.83)	0.017
Centre Rotterdam vs Leuven	1.77 (0.19-16.42)	0.61
Diagnosis group Surgery cardiac vs medical	1.65 (0.21-12.7)	0.63
Diagnosis group Surgical other vs medical	1.70 (0.41-7.06)	0.47
PELOD score (per point added)	1.03 (0.96-1.10)	0.41
PIM2 score (per point added)	1.21 (0.89-1.64)	0.22
Weight for age Z-score (per Z-score added)[a]	0.98 (0.66-1.46)	0.92

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Birthweight-for-gestational age Z-score.

Table S7-8: Multivariable linear regression analysis determining significant and independent associations between risk factors and time-to-life discharge from PICU in the neonates aged ≤1 week

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1.69 (1.16-2.46)	0.0063
Centre Rotterdam vs Leuven	0.57 (0.18-1.79)	0.33
Diagnosis group Surgery cardiac vs medical	0.98 (0.38-2.56)	0.97
Diagnosis group Surgical other vs medical	1.00 (0.54-1.88)	0.99
PELOD score (per point added)	0.97 (0.93-1.01)	0.97
PIM2 score (per point added)	0.78 (0.66-0.91)	0.0018
Weight for age Z-score (per Z-score added)[a]	1.07 (0.90-1.27)	0.44

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Birthweight-for-gestational age Z-score.

Table S7-9: Multivariable linear regression analysis determining significant and independent associations between risk factors and time-to-life weaning from ventilatory support in the neonates aged ≤1 week

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1.61 (1.10-2.35)	0.014
Centre Rotterdam vs Leuven	0.48 (0.15-1.57)	0.23
Diagnosis group Surgery cardiac vs medical	0.77 (0.30-2.01)	0.60
Diagnosis group Surgical other vs medical	0.97 (0.52-1.81)	0.92
PELOD score (per point added)	0.98 (0.94-1.02)	0.28
PIM2 score (per point added)	0.69 (0.58-0.82)	<0.0001
Weight for age Z-score (per Z-score added)[a]	1.07 (0.91-1.27)	0.41

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Birthweight-for-gestational age Z-score.

Table S7-10: Multivariable linear regression analysis determining significant and independent associations between risk factors and death during first week in the neonates aged ≤1 week

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.47 (0.04-5.83)	0.56
Centre Rotterdam vs Leuven	7.44 (0.07-773.75)	0.40
Diagnosis group Surgery cardiac vs medical	7.22 (0.07-712.22)	0.40
Diagnosis group Surgical other vs medical	1.01 (0.05-22.39)	1.00
PELOD score (per point added)	1.05 (0.94-1.17)	0.37
PIM2 score (per point added)	2.76 (1.28-5.95)	0.01
Weight for age Z-score (per Z-score added)[a]	1.94 (0.62-6.02)	0.25

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Birthweight-for-gestational age Z-score.

Table S7-11: Multivariable linear regression analysis determining significant and independent associations between risk factors and 90 day mortality in the neonates aged ≤1 week

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.31 (0.07-1.44)	0.13
Centre Rotterdam vs Leuven	5.01 (0.20-123.47)	0.32
Diagnosis group Surgery cardiac vs medical	2.58 (0.14-48.32)	0.53
Diagnosis group Surgical other vs medical	0.74 (0.08-6.79)	0.79
PELOD score (per point added)	1.09 (0.99-1.20)	0.077
PIM2 score (per point added)	1.92 (1.22-3.02)	0.0050
Weight for age Z-score (per Z-score added)[a]	0.93 (0.44-1.97)	0.86

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Birthweight-for-gestational age Z-score.

Table S7-12: Multivariable linear regression analysis determining significant and independent associations between risk factors and hypoglycaemia in the neonates aged ≤1 week

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	3.57 (1.23-10.45)	0.019
Centre Rotterdam vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	0.00 (0.00-.)	1.00
Diagnosis group Surgical other vs medical	0.35 (0.06-2.10)	0.25
PELOD score (per point added)	0.98 (0.89-1.07)	0.57
PIM2 score (per point added)	1.28 (0.88-1.86)	0.20
Weight for age Z-score (per Z-score added)[a]	0.83 (0.50-1.36)	0.45

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Birthweight-for-gestational age Z-score.

Table S7-13: Multivariable linear regression analysis determining significant and independent associations between risk factors and acquiring new infections in the neonates aged <1 day

Variable	Odds ratio (95% CI)	P-value
Randomisation Late vs Early PN	0.10 (0.01-0.64)	0.015
Centre Rotterdam vs Leuven	0.00 (0.00-.)	1.00
Diagnosis group Surgery cardiac vs medical	2.96 (0.10-92.62)	0.54
Diagnosis group Surgical other vs medical	0.57 (0.07-4.98)	0.61
PELOD score (per point added)	1.00 (0.86-1.17)	0.98
PIM2 score (per point added)	1.06 (0.64-1.75)	0.83
Weight for age Z-score (per Z-score added)[a]	1.37 (0.66-2.84)	0.40

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Birthweight-for-gestational age Z-score.

Table S7-14: Multivariable linear regression analysis determining significant and independent associations between risk factors and time-to-life discharge from PICU in the neonates aged <1 day

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	1.95 (0.93-4.12)	0.078
Centre Rotterdam vs Leuven	0.08 (0.003-2.07)	0.13
Diagnosis group Surgery cardiac vs medical	1.89 (0.34-10.47)	0.47
Diagnosis group Surgical other vs medical	2.38 (0.64-8.92)	0.20
PELOD score (per point added)	0.93 (0.82-1.05)	0.25
PIM2 score (per point added)	0.87 (0.66-1.14)	0.31
Weight for age Z-score (per Z-score added)[a]	1.06 (0.78-1.46)	0.70

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Birthweight-for-gestational age Z-score.

Table S7-15 Multivariable linear regression analysis determining significant and independent associations between risk factors and time-to-life weaning from ventilatory support in the neonates aged <1 day

Variable	Hazard ratio (95% CI)	P-value
Randomisation Late vs Early PN	2.63 (1.23-5.63)	0.013
Centre Rotterdam vs Leuven	0.09 (0.003-2.16)	0.14
Diagnosis group Surgery cardiac vs medical	1.75 (0.32-9.55)	0.52
Diagnosis group Surgical other vs medical	2.47 (0.69-8.87)	0.17
PELOD score (per point added)	0.95 (0.84-1.08)	0.44
PIM2 score (per point added)	0.74 (0.54-1.01)	0.060
Weight for age Z-score (per Z-score added)[a]	1.02 (0.74-1.40)	0.91

PN = parenteral nutrition, PELOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2.
[a]Birthweight-for-gestational age Z-score.

Chapter 4

Outcomes of Delaying Parenteral Nutrition for 1 Week vs Initiation Within 24 Hours Among Undernourished Children in Paediatric Intensive Care: A Secondary Analysis of the PEPaNIC Randomised Clinical Trial

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ABSTRACT

Importance

Undernourishment has been associated with poor outcomes of critical illness in children. The impact of withholding parenteral nutrition (PN) for 1 week in undernourished critically ill children is unknown.

Objective

To assess the outcome effects of withholding PN for 1 week in undernourished critically ill children.

Design, setting and participants

This is a secondary analysis of the randomised controlled trial Paediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (n=1440), which focused on the subgroup of paediatric intensive care unit (PICU) patients identified as undernourished upon admission. Children included in the Paediatric Early versus Late Parenteral Nutrition in Intensive Care Unit randomised controlled trial were enrolled between June 18, 2012, and July 27, 2015. Undernourishment was defined as weight-for-age Z-score less than -2 in children aged younger than1 year, and body mass index-for-age Z-score less than -2 in children 1 year or older. Data analysis was conducted from August 3 2017, to July 6 2018.

Intervention

Patients were randomised to initiation of supplemental PN within 24 hours (Early-PN) or after 1 week (Late-PN) when enteral nutrition was insufficient.

Main outcomes and measures

Primary endpoints were risk of new infections acquired in PICU and time to live PICU discharge, assessed via multivariable logistic regression and Cox proportional hazard analyses, adjusted for risk factors.

Results

A total of 289 of 1440 children (20%) were identified as undernourished, of whom 150 of 717 patients (20.9%) in the Late-PN group and 139 of 723 (19.2%) were in the Early-PN group. On admission, characteristics were similar among the treatment groups. Mean weight Z-scores were -3.33 (SD 1.18) in the Late-PN group and -3.21 (SD 1.09) in the Early-PN group. Compared with well-nourished PICU patients, undernourishment on admission was associated with lower likelihood of an earlier live PICU discharge (adjusted hazard ratio 0.86; 95% CI 0.75-0.99; p=0.03).

Among undernourished PICU patients, Late-PN reduced the risk of new infections by 11.0% (adjusted odds ratio 0.39; 95% CI 0.19-0.78; p=0.008), and shortened the duration of PICU stay with a median of 2 days (earlier live PICU discharge: adjusted hazard ratio 1.37; 95% CI 1.06-1.75; p=0.01). The safety outcomes mortality, incidence of hypoglycaemia during the first week, and incidence of weight deterioration during PICU stay were similar between the treatment groups.

Conclusion and relevance

In undernourished critically ill children, withholding PN for 1 week was clinically superior to Early-PN.

INTRODUCTION

The prevalence of undernourishment in children on admission to the paediatric intensive care unit (PICU) has been shown to be up to 24%.[42] Undernourishment on admission to the PICU has been associated with increased mortality and morbidity such as infectious complications, longer need for mechanical ventilation and prolonged hospital stay.[33,35,36] Observational cohort studies have shown that higher nutritional intake is associated with an improvement of nutritional status,[4-7] although the role of parenteral nutrition (PN) herein has not been investigated.[141] Assumptions have been made that an earlier and increased nutrition delivery might prevent deterioration of nutritional status, and subsequently improve clinical outcome.[3] This strategy is promoted more vigorously in undernourished patients where macronutrient deficiency is presumed to be more detrimental during acute illness.[74]

Recently, the Paediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC) randomized controlled trial (RCT), including 1440 critically ill children, showed that withholding PN for 1 week (Late-PN) resulted in fewer new infections and reduced the duration of PICU stay as compared with initiating PN at day 1 (Early-PN).[18] These clinical benefits were even larger in children who were at high risk of developing undernutrition, reflected by a high score on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids).[142] However, withholding PN for 1 week in undernourished critically ill children, unable to advance past low volumes of enteral nutrition (EN), raised concerns among experts.[71,74,75] Recently updated guidelines advise to start supplemental PN earlier in undernourished children than in well-nourished children if enteral intake is insufficient.[74,136] This secondary analysis of the PEPaNIC RCT investigated the impact of withholding supplemental PN in a subgroup of critically ill children who were acutely undernourished on admission to the PICU.

METHODS

Patients and procedure

These analyses were performed for children in the 3 PICUs (Belgium, The Netherlands and Canada) who participated in the PEPaNIC RCT (recruitment from June 18, 2012 to July 27, 2015). This study has followed the Consolidated Standards of 6 Reporting Trials (CONSORT) reporting guideline. The full study protocol has been reported previously.[18,129] Briefly, 1440 critically ill children (term newborns to age 17 year) with a score on the STRONGkids of 2 or higher were included. This score ranges from 0 to 5, with a higher score indicating a higher risk of developing undernutrition. The children were randomly assigned to Late-PN (withholding PN during the first week) or Early-PN (initiation of PN at day 1), if EN was <80% of target, and was expected to be insufficient for at least 24 hours. Children in the Late-PN group received a mixture of dextrose 5% and saline to match the amount of fluid administered to those in the Early-PN group. After the

first week, PN was also started in the Late-PN group if EN was less than 80% of caloric target. Initiation and incline of EN was similar between the treatment groups.[18,129] Both groups received parenteral micronutrients (vitamins, minerals and trace elements) from day 2 onwards if EN was less than 80% of the target.[18,129] Furthermore, blood glucose control with insulin according to local targets was identical in both groups.[18,129] In Leuven, Belgium, target range for blood glucose concentrations was 50 to 80 mg/dL (to convert blood glucose concentrations to millimoles per litre, multiply by 0.0555) in infants aged younger than 1 year and 70 to 100 mg/dL (to convert blood glucose concentrations to millimoles per litre, multiply by 0.0555) in older children. In Rotterdam, The Netherlands, target range for blood glucose concentration was 72 to 144 mg/dL (to convert blood glucose concentrations to millimoles per litre, multiply by 0.0555), except for patients with traumatic brain injury in which a range of 108 to 144 mg/dL (to convert blood glucose concentrations to millimoles per litre, multiply by 0.0555) was targeted. In Edmonton, Canada, insulin was administered to target blood glucose concentration less than 180 mg/dL (to convert blood glucose concentrations to millimoles per litre, multiply by 0.0555). After every change in macronutrient intake or amount of administered insulin, blood glucose concentration was checked hourly, either within routine laboratory check or by use of bedside glucose meters, until 3 consecutive measurements were within the targeted range. If a central venous line was not or no longer in place for clinical purposes, any required PN was delivered via a peripheral line.

Outcome assessors and investigators were not directly involved in the PICU and were blinded to the treatment allocation.

The institutional ethical review boards of the participating centres in Leuven Belgium (ML8052), Rotterdam, The Netherlands (NL38772.000.12) and Edmonton, Canada (Pro00038098) approved the study, which was performed in accordance with the 1964 Declaration of Helsinki and its amendments. Written informed consent was obtained from the parents or legal guardians.

For the current secondary analysis, a subgroup of acutely undernourished children on admission was identified. The broad age range of the patients in our study population did not allow us to use the same definition in all children. Therefore, acute undernutrition was defined as weight-for-age Z-score less than -2 in children aged younger than 1 year, and BMI-for-age Z-score less than -2 in children aged 1 year or older.[131,143] Severe acute undernutrition was defined as WFA Z-score <-3 in children aged <1 year, and BFA Z-score <-3 in children aged ≥1 year.[131,143]

Outcomes

Primary outcomes were the incidence of new infections during the PICU stay, and length of the PICU stay accounting for mortality as a competing risk.[129] Discharge from PICU was defined as ready for discharge from PICU (i.e. no longer need for, or at risk of, vital organ support).[129] Secondary outcomes were 7-day mortality (i.e. during the intervention window), death during

PICU stay, death during hospital stay, and 90-day mortality, incidence of hypoglycaemia (blood glucose <40 mg/dl [to convert blood glucose concentrations to millimoles per litre, multiply by 0.0555]) during the first week, incidence of weight Z-score deterioration during PICU stay (defined as a negative change in weight Z-score from admission to PICU discharge), duration of mechanical ventilatory support, and length of hospital stay.

Statistical analyses

The analyses were done based on intention-to-treat. Variables are reported as proportions, mean (SD) if normally distributed or as median (interquartile range) if not-normally distributed. Proportions were analysed univariably using χ^2 test, means with t-test and medians with Mann Whitney U test. PICU stay, hospital stay and duration of mechanical ventilation were investigated univariably as the crude number of days, and multivariably as the likelihood of an earlier discharge from PICU alive, likelihood of an earlier discharge from hospital alive and likelihood of an earlier weaning from mechanical ventilation alive, respectively. The results on time to PICU discharge alive, time to hospital discharge alive and time to weaning from mechanical ventilation alive can potentially be biased by the rate of mortality. Therefore, these multivariable time-to-event effect sizes were calculated with the use of Cox proportional hazard analysis, with data of survivors censored at 90 days, and data of non-survivors was set beyond all survivors at 91 days to account for mortality as competing risk. The multivariable analyses of dichotomized outcomes were performed using logistic regression. Odds ratios or hazard ratios with 95% confidence intervals were calculated. Multivariable analyses were adjusted for the baseline risk factors centre, age, diagnosis group, STRONGkids category,[142] Paediatric Logistic Organ Dysfunction score,[144] and Paediatric Index of Mortality 2 score.[145]

P-values 0.05 or less were considered statistically significant and all tests were 2-sided. All analyses were performed with IBM SPSS Statistics, version 21 (IBM Corp). Z-scores were calculated with the use of Growth Analyzer Research Calculation Tool, version 4.[146]

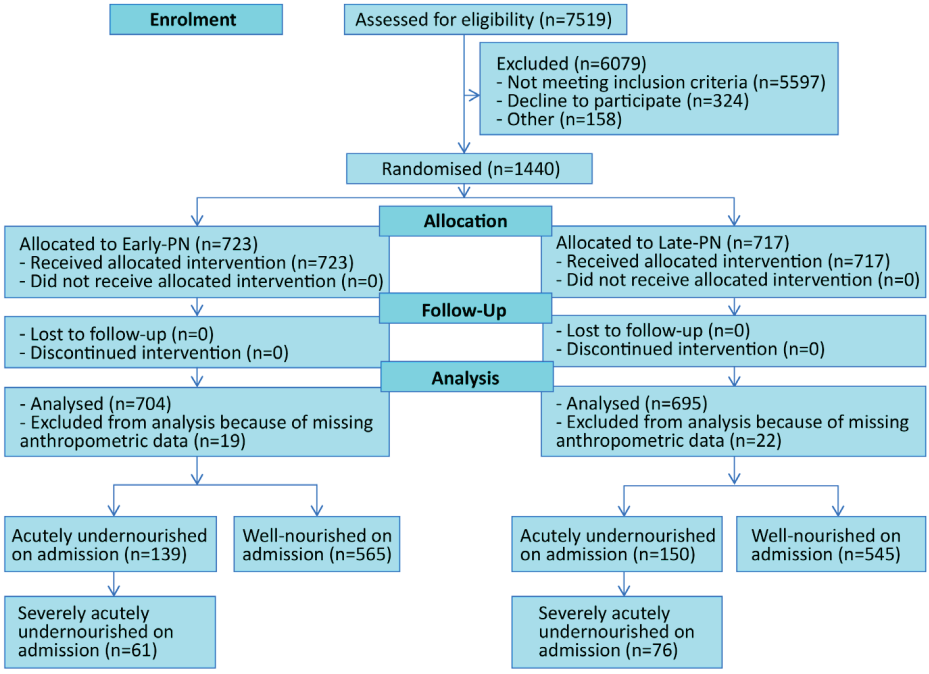
RESULTS

Patients undernourished on PICU admission

In total, 289 of 1440 children (20%) were acutely undernourished on admission, among which 150 of 717 patients (20.9%) were assigned to the Late-PN group, and 139 of 723 patients (19.2%) were assigned to the Early-PN group (Figure 1). The incidence of undernourishment on admission was similar in all centres, 21.3% in Leuven, Belgium, 19.5% in Rotterdam, The Netherlands, and 21.9% in Edmonton, Canada (p=0.70). In total, 18.5% of the children with a medium risk score on the STRONGkids tool were undernourished versus 38.9% of the children with a high risk score (p<0.001). Baseline characteristics for the undernourished children were similar for the Late-PN group and the Early-PN group (Table 1). The weight Z-score on PICU admission was -3.33 (SD

1.18) in the Late-PN group and -3.21 (SD 1.09) in the Early-PN group (Table 1). Enteral energy and macronutrient doses were similar in both treatment groups; whereas, parenteral energy and macronutrient doses differed between the treatment groups, which showed adherence to the protocol (Appendix). At the time PN was initiated in the Early-PN group, more than 95% of critically ill children received less than 50% of caloric targets enterally.[147,148] During the intervention period, 55 children (35.7%) in the Late-PN group, and 43 children (30.9%) in the Early-PN group did not receive any EN (p=0.30).

Figure 1: Flow diagram of children with and without undernourishment on PICU admission



DNR = do not resuscitate; PICU = paediatric intensive care unit; NICU = neonatal intensive care unit; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth, range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

Acutely undernourished is defined as weight-for-age Z-score <-2 (if <1 year), or BMI-for-age Z-score <-2 (if ≥1 year).[131,143] Severely acutely undernourished is defined as weight-for-age Z-score <-3 (if <1 year), or BMI-for-age Z-score <-3 (if ≥1 year).[131,143]

Undernourished versus well-nourished children

Comparison of baseline characteristics between undernourished and well-nourished children showed that the group of undernourished children was younger, contained a higher proportion of respiratory diagnoses and lower proportion of neurosurgical diagnoses on PICU admission, and comprised a lower proportion of children needing mechanical hemodynamic support (Appendix).

Being undernourished on admission was not associated with an increased risk of acquiring a new infection in the PICU, but was associated with both a prolonged duration of PICU stay and hospital stay with a median difference of 2 days and a lower likelihood of an earlier discharge from PICU alive (adjusted hazard ratio 0.86; 95% CI 0.75-0.99; p=0.03), as well as a lower likelihood of an earlier discharge from hospital alive (adjusted hazard ratio 0.83; 95% CI 0.73-0.96; p=0.01) (Appendix).

Undernourishment on admission was associated with a lower 7-day mortality, but a higher incidence of hypoglycaemia during the first week as compared with well-nourished children. Death during PICU stay and hospital stay, and 90-day mortality were not associated with undernourishment on admission (Appendix).

Late-PN versus Early-PN in children undernourished upon PICU admission

In children who were undernourished on admission to the PICU, Late-PN reduced the risk of new infections with an absolute 11.0% (22.3% vs. 11.3%, p=0.02), with an adjusted odds ratio for new infections of 0.39 (95% CI 0.19-0.78; p=0.01). Late-PN also shortened the duration of PICU dependency with a median of 2 days in undernourished children (6 vs 4 days; p=0.01), with a higher likelihood of an earlier discharge from PICU alive (adjusted hazard ratio 1.37; 95% CI 1.06-1.75; p=0.01; Table 2).

Safety outcomes mortality at all investigated time-points and the incidence of hypoglycaemia did not differ between Late-PN and Early-PN in the undernourished children (Table 2). The duration of mechanical ventilatory support was shorter in the Late-PN group, with a higher likelihood of being weaned alive earlier from mechanical ventilation (adjusted hazard ratio 1.39; 95% CI 1.09-1.77; p=0.008; Table 2). Late-PN also shortened the duration of hospital stay with a median of 4 days, with a higher likelihood of an earlier discharge alive (adjusted hazard ratio 1.37; 95% CI 1.07-1.75; p=0.01; Table 2). In a subgroup of 100 undernourished critically ill children with weight Z-scores on admission and at discharge from the PICU available, of which 48 in the Late-PN group and 52 in the Early-PN group, the incidence of weight Z-score deterioration was not different between the treatment groups (Table 2). A sensitivity analysis, assuming that all patients who died in the PICU had acquired a new infection during their PICU stay, supported our results; Late-PN reduced the risk of new infections with an absolute 9.7% (23.7% vs. 14.0%, p=0.03), with an adjusted odds ratio for new infections of 0.46 (95% CI 0.24-0.91; p=0.03).

Table 1: Baseline characteristics of children undernourished on admission

Characteristic	Early-PN (n=139)	Late-PN (n=150)	P-value
Male	88 (63.3)	85 (56.7)	0.28
Age at randomisation, median (IQR), y	0.43 (0.25-2.36)	0.46 (0.21-3.46)	0.69
High STRONGkids category	27 (19.4)	31 (20.7)	0.88
Weight Z-score, mean (SD)[a]	-3.21 (1.09)	-3.33 (1.18)	0.37
Severely undernourished on admission[b]	61 (43.9)	76 (50.7)	0.25
PELOD score, median (IQR)	21 (11-32)	21 (12-31)	0.99
PIM2 score, mean (SD)	-2.46 (1.52)	-2.47 (1.69)	0.93
Risk of Mortality, median (IQR), %[c]	6.3 (2.8-22.8)	6.7 (2.5-15.7)	0.58
Diagnostic group			0.72
Surgical			
Abdominal	7 (5.0)	10 (6.7)	
Burns	0 (0.0)	0 (0.0)	
Cardiac	58 (41.7)	66 (44.0)	
Neurologic	6 (4.3)	6 (4.0)	
Thoracic	3 (2.2)	2 (1.3)	
Transplant	0 (0.0)	2 (1.3)	
Trauma/orthopedic	8 (5.8)	9 (6.0)	
Other	5 (3.6)	1 (0.7)	
Medical			
Cardiac	6 (4.3)	6 (4.0)	
Gastro-intestinal/hepatic)	0 (0.0)	2 (1.3)	
Hematologic/oncologic	1 (0.7)	1 (0.7)	
Neurologic	11 (7.9)	9 (6.0)	
Renal	0 (0.0)	0 (0.0)	
Respiratory	29 (20.9)	28 (18.7)	
Other	5 (3.6)	8 (5.3)	
Syndrome or genetic abnormality			0.36
No	96 (69.1)	94 (62.7)	
Yes	36 (25.9)	43 (28.7)	
Suspected	7 (5.0)	13 (8.7)	
Mechanical ventilatory support on PICU admission	124 (89.2)	127 (84.7)	0.30
Inotrope or vasopressor medication on PICU admission	57 (41.0)	69 (46.0)	0.41
Mechanical hemodynamic support on PICU admission	0 (0.0)	3 (2.0)	0.25

PELOD = Paediatric Logistic Organ Dysfunction, range from 0 to 71, with higher scores indicating more severe illness; PICU = paediatric intensive care unit; PIM2 = Paediatric Index of Mortality 2, with higher scores indicating a higher risk of mortality; PN = parenteral nutrition; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth, range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[a]<1 year: weight-for-age Z-score, ≥1 year: BMI-for-age Z-score.[131,143]

[b]Severe undernutrition defined as: <1 year: weight-for-age Z-score <-3, ≥1 year: BMI-for-age Z-score <-3.[131,143]

[c]Based on PIM2 score =([exp (PIM2)]/[1+exp (PIM2)])*100%.

Table 2: Outcomes of Late-PN versus Early-PN in children undernourished on admission

Outcome	Early-PN (n=139)	Late-PN (n=150)	P-value	Adjusted OR or HR (95% CI)[a]	Adjusted P-value*
Primary endpoint					
New infections	31 (22.3)	17 (11.3)	0.02	0.39 (0.19-0.78)[b]	0.01
Airway	16 (11.5)	8 (5.3)	0.09		
Bloodstream	7 (5.0)	2 (1.3)	0.09		
Urinary tract	1 (0.7)	0 (0.0)	0.48		
Soft Tissue	1 (0.7)	1 (0.7)	>0.99		
No focus identified	4 (2.9)	4 (2.7)	>0.99		
Other focus	2 (1.4)	2 (1.4)	0.94		
Duration of PICU stay median (IQR), d	6 (3-11)	4 (2-8)	0.01	1.37 (1.06-1.75)	0.01
Secondary safety endpoint					
Death during first week	1 (0.7)	1 (0.7)	>0.99	0 (0->100)[b]	0.35
Death during PICU stay	5 (3.6)	5 (3.3)	0.90	0.70 (0.16-3.77)[b]	0.75
Death during hospital stay	9 (6.5)	7 (4.7)	0.50	0.58 (0.17-1.97)[b]	0.39
90-day mortality	9 (6.5)	8 (5.3)	0.80	0.74 (0.23-2.34)[b]	0.60
Hypoglycemia (blood glucose <40 mg/dL) during first week after randomisation	12 (8.6)	20 (13.3)	0.26	1.74 (0.75-4.06)[b]	0.20
Deterioration of weight Z-score during PICU stay[c]	30 (57.7)	23 (47.9)	0.33	0.60 (0.25-1.41)[b]	0.24
Secondary efficacy endpoint					
Duration of mechanical ventilatory support, median (IQR), d	3 (2-7)	2.5 (1-5)	0.10	1.39 (1.09-1.77)	0.01
Duration of hospital stay, median (IQR), d	14 (8-30)	10 (7-22)	0.03	1.37 (1.07-1.75)	0.01

PELOD = Paediatric Logistic Organ Dysfunction, range from 0 to 71, with higher scores indicating more severe illness; PICU = paediatric intensive care unit; PIM2 = Paediatric Index of Mortality 2, with higher scores indicating a higher risk of mortality; PN = parenteral nutrition; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth, range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[a]Odds ratio (OR) or Hazard ratio (HR), adjusted for baseline risk factors center, age, diagnosis group, PELOD score, PIM2 score, and STRONGkids category, with corresponding 95% Confidence Interval (CI).

[b]These values are adjusted Odds Ratios, the other values are adjusted Hazard Ratios.

[c]Available in 100 children, of which 52 in the Early-PN group and 48 in the Late-PN group.

Table 3: Outcomes of Late PN versus Early PN in severely acutely undernourished children

Outcome	Early-PN (n=61)	Late-PN (n=76)	P-value	Adjusted OR or HR (95% CI)[a]	P-value[a]
Primary endpoint					
New infections	11 (18.0)	8 (10.5)	0.21	0.33 (0.09-1.27)[b]	0.11
Duration of PICU stay, median (IQR), d	5 (3-8)	4 (2-6)	0.05	1.49 (1.04-2.13)	0.03
Secondary safety endpoint					
Death during first week	0 (0)	1 (1.3)	0.37	>100 (0.00-x)[b]	>0.99
Death during PICU stay	1 (1.6)	2 (2.6)	0.69	0.05 (0->100)[b]	0.60
Death during hospital stay	3 (4.9)	4 (5.3)	0.93	0.40 (0.05-3.28)[b]	0.39
90-day mortality	3 (4.9)	4 (5.3)	0.93	0.25 (0.02-2.77)[b]	0.26
Hypoglycaemia (blood glucose <40 mg/dl) during first week after randomisation	6 (9.8)	9 (11.8)	0.71	2.02 (0.39-10.41)[b]	0.40
Weight Z-score deterioration	17 (63.0)	15 (55.6)	0.58	0.69 (0.21-2.36)[b]	0.56
Secondary efficacy endpoint					
Duration of mechanical ventilatory support, median (IQR), d	2 (2-7.5)	3 (1.25-5)	0.30	1.43 (0.99-2.05)	0.06
Duration of hospital stay, median (IQR), d	15 (7.5-28)	10 (7-22)	0.14	1.38 (0.96-2.00)	0.09

PELOD = Paediatric Logistic Organ Dysfunction, range from 0 to 71, with higher scores indicating more severe illness; PICU = paediatric intensive care unit; PIM2 = Paediatric Index of Mortality 2, with higher scores indicating a higher risk of mortality; PN = parenteral nutrition; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth, range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

Severely acutely undernourished defined as weight-for-age Z-score <-3 (if <1 year), or BMI-for-age Z-score <-3 (if ≥1 year)[131,143]

[a]Odds ratio (OR) or Hazard ratio (HR), adjusted for baseline risk factors center, age, diagnosis group, PELOD score, PIM2 score, and STRONGkids category, with corresponding 95% Confidence Interval (CI).

[b]These values are adjusted ORs, the other values are adjusted HRs.

Late-PN versus Early-PN in children severely undernourished upon PICU admission

In the Late-PN group, 76 of 717 children (10.6%) were severely undernourished, and 61 of 723 children (8.4%) in the Early-PN group (Figure 1). Among severely undernourished children, the baseline characteristics were similar between the treatment groups (Appendix). In severely undernourished children, Late-PN shortened the duration of PICU stay significantly with a median difference of 1 day, both in univariable and multivariable analyses corrected for baseline risk factors (Table 3). The percentage of severely undernourished children with a new infection was 10.5% in the group receiving Late-PN, as compared with 18.0% in the group receiving Early-PN, although this difference was not statistically significant. The safety outcomes were not significantly different between the treatment groups (Table 3).

DISCUSSION

Overall, we found that approximately 20% of the children in the PEPaNIC study were acutely undernourished on PICU admission and that these children performed worse with a lower likelihood of earlier discharge from PICU alive as well as from the hospital as compared with well-nourished children. The undernourished children benefited from withholding PN during the first week of critical illness compared to initiating PN at the first day, as illustrated by a decreased risk of new infections, a shorter dependency on intensive care and an accelerated discharge from the hospital alive. The benefits of Late-PN were noticeable irrespective of centre, age, disease severity, risk of mortality, diagnosis group, and STRONGkids score on admission. Late-PN did not affect the safety outcomes mortality and incidence of hypoglycaemia, and was not associated with weight deterioration in the undernourished critically ill children.

The association between undernourishment and worse clinical outcome, as in our study demonstrated by longer duration of PICU and hospital stay, has previously been described.[33,35,36] However, baseline characteristics and diagnoses on admission in undernourished children differed from those in well-nourished children, which could have explained these differences in outcomes. Therefore, we cannot rule out that other factors played a role in the clinical outcome of children who are undernourished on admission.

The large proportion of undernourished children on admission to the PICU, as well as the ongoing weight loss during PICU admission agree with previous studies.[4,43] However, the beneficial effect of withholding PN during the first week of critical illness in these undernourished children contrasts with concerns raised by experts.[71,75,136] The effect sizes of Late-PN versus Early-PN in the undernourished group were even higher than in the main trial cohort, which is in line with the larger effect size in critically ill children with a high STRONGkids score.[18] In a small subgroup of severely undernourished children, Late-PN resulted in a significant higher likelihood of earlier discharge from PICU alive as compared with Early-PN. Although the proportions of new infections were in line with those found in the main trial cohort,[18] the risk of acquiring a new

infection was not statistically different between the randomization arms, probably owing to lack of power in this small subgroup. Although speculative, a possible explanation for these somewhat counterintuitive results of withholding PN in undernourished children, who are considered to be vulnerable for low nutritional intake, could be an attenuated immunosuppression. Undernourished children already have an altered immune system.[149] Moreover, critical illness induces further immunosuppression,[150] and Early-PN may potentially reduce immune function.[151-153] An important function of the immune system is autophagy, an adaptive response to critical illness in order to control the cellular damage. In rabbits[132] and critically ill adults,[55] Late-PN enhanced autophagy as compared with Early-PN. Hence, possibly, undernourished critically ill children may have an immune response which differs from well-nourished critically ill children making them even more susceptible for the benefits of withholding PN during the acute phase.

In contrast to the data from our randomised study, in non-randomised observational cohort studies a lower nutritional intake, with or without PN, was associated with excessive weight deterioration.[4-7] We cannot exclude that the different results between these observational studies and our study are related to the parenteral route of nutrition for which we randomised, although EN in our study was provided equally to both groups, both in timing of initiation as well as amounts. Nonetheless, we should consider the possibility that parenteral nutritional support during the acute phase of critical illness in children is not capable to influence the children's nutritional status assessed with anthropometric measurements. Hence, the deterioration of the nutritional status during acute critical illness appears primarily determined by the diagnosis and disease severity with which the child presents to the PICU and appears unaffected by parenteral nutritional support during the acute phase. The inflammatory response during critical illness possibly needs to be resolved before the child can transit into an anabolic state.[154] Future research is warranted to determine when a patient transits from the acute phase to a stable or even recovery phase and whether and how in these phases parenteral nutritional support is able to improve the nutritional status and long-term outcomes of the patient.[10]

However, our findings are reassuring with respect to the concerns raised by experts about the consequence of Late-PN in undernourished critically ill children.[71,74,75] Late-PN was effective, and did not negatively affect mortality, hypoglycaemia or change in weight Z-score as compared with Early-PN. Hence, there appears to be no support for early supplementation of PN during acute critical illness to improve outcomes or to reverse or prevent weight deterioration in the PICU in undernourished critically ill children.

Our study has some limitations. First, in children younger than 2 years with a history of being born prematurely, we were unable to use corrected ages to calculate weight-for-age and body mass index-for-age Z-scores. Consequently, the proportion of undernourished children may be overestimated, although such overestimation would be equal in both treatment groups owing to the randomised design. Second, weight measured in the PICU is highly influenced by factors

such as fluid overload, tubes, and splints. Therefore, a change in weight during admission does not always reflect a change in lean body mass. Other measurements, such as mid-upper arm circumference, might be a more reliable measure, as this is less affected by fluid change and extracorporeal items attached to the child. Despite these challenges to reliably measure the change in nutritional status, the inaccuracies in the anthropometric data will most likely be distributed equally in both treatment groups, owing to the randomised design. Furthermore, the amount of administered fluid was similar in the 2 groups. Third, as longitudinal anthropometric measurements were only available in part of the undernourished children, there may be a selection bias. Fourth, we only presented short-term outcome measures. Follow-up of our patients, which is currently ongoing, has to point out the long-term effects of withholding PN.

CONCLUSIONS

Critically ill children who are undernourished on PICU admission have a lower likelihood of an earlier discharge from PICU and hospital alive as compared with well-nourished children. Withholding PN during the first week in these acutely undernourished critically ill children was clinically superior to supplementing PN early, with a lower risk of new infections and a higher likelihood of an earlier discharge alive. Withholding PN during the first week was not associated with weight deterioration during PICU stay.

APPENDIX

Methods S1: Protocol for scoring of infections

Data export

All patients receiving antimicrobial agents were identified by the data manager, who provided an export of all patient numbers with all the information on antimicrobial agents given as well as the duration of such treatment.

Identification of patients with infections

The infectious disease specialists, who were blinded for treatment allocation, selected all patients receiving antimicrobial agents for more than 48h, after excluding all patients who received prophylaxis. Each patient who fulfilled the criteria for infection, as well as the type of infection, was identified as such based on thorough review of the medical record.[155] Patients for whom antimicrobials where initiated prior to PICU admission or within the first 48 hours of admission while the criteria for infection were fulfilled, were labelled as "having an infection upon admission". When antimicrobial agents were initiated after randomization and beyond the first 48 hours in the PICU, and were given for more than 48 hours while the criteria for infection were fulfilled, the patient was labelled as "having a new infection".[18,155]

Table S1: Energy and macronutrient administration in undernourished children for the first 7 days in PICU

		n		Total dose		Enteral dose		Parenteral dose	
	Day	Early-PN	Late-PN	Early-PN	Late-PN	Early-PN	Late-PN	Early-PN	Late-PN
Energy	1	139	150	23.5 (13.3-33.4)	5.3 (3.7-8.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	22.3 (13.3-30.9)	5.2 (3.6-7.5)
(kcal/kg)	2	127	129	52.8 (45.2-66.3)	11.6 (8.2-29.6)	0.0 (0.0-23.5)	0.0 (0.0-20.1)	48.8 (27.7-54.8)	8.4 (6.1-10.6)
	3	106	105	74.0 (55.2-90.7)	27.6 (12.0-58.9)	4.1 (0.0-43.4)	14.4 (0.0-49.6)	54.8 (20.2-73.2)	8.0 (4.5-10.8)
	4	98	85	82.3 (60.6-101.0)	35.9 (20.1-70.5)	14.8 (0.0-59.3)	21.7 (0.0-67.4)	45.5 (16.4-84.4)	6.4 (2.4-12.0)
	5	84	68	93.8 (59.0-107.5)	42.8 (22.1-85.7)	25.1 (0.0-77.2)	37.7 (6.3-85.4)	38.1 (6.3-85.7)	5.4 (1.4-10.7)
	6	70	56	92.1 (60.6-102.3)	55.6 (21.6-82.9)	23.5 (0.0-70.3)	49.3 (10.0-82.3)	35.9 (2.8-95.8)	5.1 (1.4-10.3)
	7	62	44	98.3 (73.6-105.6)	52.6 (21.1-97.5)	42.1 (3.6-91.2)	44.2 (0.0-88.9)	25.4 (1.9-90.3)	4.8 (0.6-12.3)
Glucose	1	139	150	4.9 (3.3-6.9)	1.3 (0.9-2.1)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	4.6 (3.3-6.4)	1.3 (0.9-1.9)
(g/kg)	2	127	129	9.8 (6.9-11.6)	2.8 (2.0-4.6)	0.0 (0.0-2.2)	0.0 (0.0-2.1)	8.9 (4.6-10.5)	2.1 (1.5-2.6)
	3	106	105	10.0 (7.3-12.4)	4.6 (2.7-7.6)	0.0 (0.0-5.0)	1.3 (0.0-4.9)	7.2 (2.8-11.3)	2.0 (1.1-2.7)
	4	98	85	10.0 (7.6-13.6)	5.6 (3.0-8.8)	1.2 (0.0-6.5)	2.5 (0.0-7.4)	5.8 (1.7-12.2)	1.6 (0.6-3.0)
	5	84	68	11.5 (7.6-14.8)	6.3 (3.8-9.9)	2.5 (0.0-8.0)	3.8 (0.6-9.5)	5.0 (1.1-11.8)	1.4 (0.4-2.7)
	6	70	56	11.5 (7.7-14.0)	5.9 (3.8-9.4)	2.1 (0.0-7.8)	4.4 (0.7-8.8)	4.9 (0.7-13.2)	1.3 (0.4-2.4)
	7	62	44	11.8 (8.9-14.6)	6.5 (3.6-10.8)	5.2 (0.2-9.4)	4.7 (0.0-9.4)	3.5 (0.5-11.9)	1.2 (0.1-2.9)
Amino acids	1	139	150	0.8 (0.0-1.4)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.8 (0.0-1.4)	0.0 (0.0-0.0)
(g/kg)	2	127	129	2.1 (1.5-2.4)	0.0 (0.0-0.5)	0.0 (0.0-0.5)	0.0 (0.0-0.5)	2.0 (0.7-2.3)	0.0 (0.0-0.0)
	3	106	105	2.3 (1.7-2.6)	0.4 (0.0-1.3)	0.0 (0.0-1.1)	0.2 (0.0-1.2)	1.8 (0.2-2.4)	0.0 (0.0-0.0)
	4	98	85	2.1 (1.5-2.4)	0.7 (0.0-1.7)	0.3 (0.0-1.5)	0.7 (0.0-1.6)	1.1 (0.1-2.0)	0.0 (0.0-0.0)
	5	84	68	2.1 (1.8-2.5)	0.9 (0.1-2.0)	0.5 (0.0-1.9)	0.9 (0.1-2.0)	1.2 (0.0-2.0)	0.0 (0.0-0.0)
	6	70	56	2.0 (1.7-2.5)	1.1 (0.2-2.0)	0.5 (0.0-1.7)	1.1 (0.1-1.9)	1.3 (0.0-2.0)	0.0 (0.0-0.0)
	7	62	44	2.0 (1.8-2.6)	1.3 (0.2-2.2)	1.0 (0.0-2.1)	1.1 (0.0-2.1)	0.8 (0.0-2.0)	0.0 (0.0-0.0)
Lipid	1	139	150	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
(g/kg)	2	127	129	0.6 (0.2-1.8)	0.0 (0.0-1.1)	0.0 (0.0-1.1)	0.0 (0.0-1.0)	0.2 (0.0-0.5)	0.0 (0.0-0.0)
	3	106	105	2.3 (1.6-3.5)	0.4 (0.0-2.4)	0.0 (0.0-2.1)	0.4 (0.0-2.2)	1.5 (0.2-1.9)	0.0 (0.0-0.0)
	4	98	85	3.1 (2.0-4.0)	1.1 (0.0-3.5)	0.5 (0.0-3.0)	0.9 (0.0-3.5)	1.6 (0.1-2.8)	0.0 (0.0-0.0)
	5	84	68	3.4 (2.0-4.5)	1.6 (0.2-4.1)	1.3 (0.0-4.0)	1.5 (0.2-4.1)	1.3 (0.0-2.4)	0.0 (0.0-0.0)
	6	70	56	3.1 (2.0-4.3)	2.0 (0.3-4.2)	0.8 (0.0-3.3)	2.0 (0.3-4.2)	1.2 (0.0-2.8)	0.0 (0.0-0.0)
	7	62	44	3.3 (2.2-5.1)	2.5 (0.4-4.8)	1.7 (0.1-4.5)	2.2 (0.0-4.8)	0.8 (0.0-2.9)	0.0 (0.0-0.0)

Data represent medians and interquartile ranges. PICU = paediatric intensive care unit; PN = parenteral nutrition.
All total doses (except lipids administered on day 1) and parenteral doses of energy, glucose, amino acids, and lipids were significantly different for patients in the Early-PN and Late-PN groups, whereas no significant differences were observed for enteral doses. N indicates the number of patients still in PICU on the respective days.

Table S2: Baseline characteristics of undernourished versus well-nourished children

Characteristic	Undernourished[a] (n=289)	Well-nourished (n=1110)	P-value
Male	173 (59.9)	634 (57.1)	0.40
Age at randomisation, median (IQR), years	0.44 (0.22;2.82)	1.78 (0.24;6.74)	<0.001
High STRONGkids category	58 (20.1)	91 (8.2)	<0.001
Weight Z-score,median (IQR)[b]	-2.98 (-3.71;-2.43)	-0.15 (-0.95;0.66)	<0.001
PELOD score, median (IQR)	21 (11;32)	21 (11;31)	0.36
PIM2 score, mean (SD)	-2.47 (1.61)	-2.53 (1.74)	0.56
Risk of mortality, median (IQR), (%)[c]	6.4 (2.6-17.0)	5.7 (2.5-17.3)	0.28
Diagnostic group			<0.001
Surgical			
Abdominal	18 (6.2)	92 (8.3)	
Burns	0 (0.0)	7 (0.6)	
Cardiac	124 (42.9)	423 (38.1)	
Neurosurgery	12 (4.2)	101 (9.1)	
Thoracic	5 (1.7)	55 (5.0)	
Transplant	2 (0.7)	22 (2.0)	
Trauma/orthopedic	16 (5.5)	36 (3.2)	
Other	6 (2.1)	42 (3.8)	
Medical			
Cardiac	12 (4.2)	48 (4.3)	
Gastro-intestinal/hepatic	2 (0.7)	4 (0.4)	
Hematologic/oncologic	2 (0.7)	13 (1.2)	
Neurologic	20 (6.9)	76 (6.8)	
Renal	0 (0.0)	2 (0.2)	
Respiratory	57 (19.7)	123 (11.1)	
Other	13 (4.5)	66 (5.9)	
Mechanical ventilation on PICU admission	251 (86.9)	980 (88.3)	0.50
Inotrope or vasopressor medication on PICU admission	126 (43.6)	455 (41.0)	0.42
Mechanical hemodynamic support on PICU admission	3 (1.0)	39 (3.5)	0.03

PELOD = Paediatric Logistic Organ Dysfunction, range from 0 to 71, with higher scores indicating more severe illness; PICU = paediatric intensive care unit; PIM2 = Paediatric Index of Mortality 2, with higher scores indicating a higher risk of mortality; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth, range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[a]Acutely undernourished defined as weight-for-age Z-score <-2 if <1 year, or BMI-for-age Z-score <-2 if ≥1 year.[131,143]

[b]<1 year: weight-for-age Z-score, ≥1 year: BMI-for-age Z-score.[131,143]

[c]Based on PIM2 score =([exp (PIM2)]/[1+exp (PIM2)])*100%.

Table S3: Main outcomes of undernourished versus well-nourished children

Outcome	Undernourished[a] (n=289)	Well-nourished (n=1110)	P-value	Adjusted OR or HR (95% CI)[b]	P-value[b]
Primary endpoint					
New infections	48 (16.6)	161 (14.5)	0.37	1.23 (0.84-1.79)[c]	0.29
Duration of PICU stay — median (IQR), d	5 (2-9)	3 (2-8)	<0.001	0.86 (0.75-0.99)	0.03
Secondary safety endpoint					
Death during first week	2 (0.7)	33 (3.0)	0.03	0.10 (0.01-0.80)[c]	0.03
Death during PICU stay	10 (3.5)	53 (4.8)	0.34	0.82 (0.35-1.89)[c]	0.63
Death during hospital stay	16 (5.5)	65 (5.9)	0.84	1.14 (0.59-2.23)[c]	0.70
90-day mortality	17 (5.9)	65 (5.9)	0.99	1.29 (0.67-2.48)[c]	0.45
Hypoglycaemia (blood glucose <40 mg/dl) during first week after randomisation	32 (11.1)	67 (6.0)	0.003	1.65 (1.01-2.70)[c]	0.05
Secondary efficacy endpoint					
Duration of mechanical ventilatory support — median (IQR), d	3 (2-6)	2 (1-5)	<0.001	0.90 (0.79-1.03)	0.13
Duration of hospital stay — median (IQR), d	12 (7-26.5)	10 (6-22)	0.003	0.83 (0.73-0.96)	0.01

PELOD = Paediatric Logistic Organ Dysfunction, range from 0 to 71, with higher scores indicating more severe illness; PICU = paediatric intensive care unit; PIM2 = Paediatric Index of Mortality 2, with higher scores indicating a higher risk of mortality; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth, range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[a]Acutely undernourished defined as weight-for-age Z-score <-2 if <1 year, or BMI-for-age Z-score <-2 if ≥1 year.[131,143]

[b]Odds ratio (OR) or Hazard ratio (HR), adjusted for randomisation group, centre, age, diagnosis group, PELOD score, PIM2 score, and STRONGkids category, with corresponding 95% Confidence Interval (CI).

[c]These values are adjusted ORs, the other values are adjusted HRs.

Table S4: Baseline characteristics of children severely undernourished[a] on admission in the Early-PN and Late-PN group

Characteristic	Early-PN (n=61)	Late-PN (n=76)	P-value
Male	43 (70.5)	52 (68.4)	0.79
Age at randomisation, median (IQR), y	0.37 (0.21-0.63)	0.40 (0.20-2.52)	0.34
High STRONGkids category	15 (24.6)	17 (22.4)	0.76
Weight Z-score, mean (SD)[b]	-4.19 (0.94)	-4.17 (1.13)	0.90
PELOD score, median (IQR)	14 (6.5-32)	21.5 (12-31)	0.72
PIM2 score, mean (SD)	-2.79 (1.47)	-2.47 (2.03)	0.30
Risk of Mortality, median (IQR), (%)[c]	5.6 (2.0-20.3)	5.7 (2.5-16.6)	0.62
Diagnostic group			0.51
Surgical			
Abdominal	4 (6.6)	8 (10.5)	
Burns	0 (0)	0 (0)	
Cardiac	27 (44.3)	30 (39.5)	
Neurologic	1 (1.6)	4 (5.3)	
Thoracic	1 (1.6)	0 (0)	
Transplant	0 (0)	0 (0)	
Trauma/orthopedic	3 (4.9)	5 (6.6)	
Other	3 (4,1)	1 (1.3)	
Medical			
Cardiac	2 (3.3)	2 (2,6)	
Gastro-intestinal/hepatic	0 (0)	1 (1.3)	
Hematologic/oncologic	0 (0)	0 (0)	
Neurologic	5 (8.2)	5 (6.6)	
Renal	0 (0)	0 (0)	
Respiratory	15 (24.6)	16 (21.1)	
Other	0 (0)	4 (5.3)	
Syndrome or genetic abnormality			0.18
No	42 (68.9)	42 (55.3)	
Yes	17 (27.9)	27 (35.5)	
Suspected	2 (3.3)	7 (9.2)	
Mechanical ventilatory support on PICU admission	53 (86.9)	64 (84.2)	0.66
Inotrope or vasopressor medication on PICU admission	26 (42.6)	32 (42.1)	0.95
Mechanical hemodynamic support on PICU admission	0 (0)	1 (1.3)	0.37

PELOD = Paediatric Logistic Organ Dysfunction, range from 0 to 71, with higher scores indicating more severe illness; PIM2 = Paediatric Index of Mortality 2, with higher scores indicating a higher risk of mortality; PN = parenteral nutrition; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth, range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[a]Severely acutely undernourished defined as weight-for-age Z-score <-3 if <1 year, or BMI-for-age Z-score <-3 if ≥1 year.[131,143]

[b]<1 year: weight-for-age Z-score, ≥1 year: BMI-for-age Z-score.[131,143]

[c]Based on PIM2 score =([exp (PIM2)]/[1+exp (PIM2)])*100%.

Table S5: Baseline characteristics of children well-nourished on admission in the Early-PN and Late-PN group

Characteristic	Early-PN (n=565)	Late-PN (n=545)	P-value
Male	315 (55.8)	319 (58.5)	0.35
Age at randomisation, median (IQR), years	1.81 (0.28-6.32)	1.77 (0.19-7.32)	0.77
High STRONGkids category)	51 (9.0)	40 (7.3)	0.31
Weight Z-score, mean (SD)[a]	-0.07 (1.13)	-0.01 (1.37)	0.44
PELOD score, median (IQR)	21 (11-31)	21 (11-31)	0.98
PIM2 score, mean (SD)	-2.49 (1.75)	-2.58 (1.73)	0.37
Risk of Mortality, median (IQR), (%)[b]	5.8 (2.4-18.8)	5.5 (2.5-16.2)	0.51
Diagnostic group			0.83
Surgical			
Abdominal	45 (8.0)	47 (8.6)	
Burns	3 (0.5)	4 (0.7)	
Cardiac	221 (39.1)	202 (37.1)	
Neurologic	56 (9.9)	45 (8.3)	
Thoracic	30 (5.3)	25 (4.6)	
Transplant	7 (1.2)	15 (2.8)	
Trauma/orthopedic	19 (3.4)	17 (3.1)	
Other	16 (2.8)	26 (4.8)	
Medical			
Cardiac	23 (4.1)	25 (4.6)	
Gastro-intestinal/hepatic	2 (0.4)	2 (0.4)	
Hematologic/oncologic	7 (1.2)	6 (1.1)	
Neurologic	35 (6.2)	41 (7.5)	
Renal	1 (0.2)	1 (0.2)	
Respiratory	65 (11.5)	58 (10.6)	
Other	35 (6.2)	31 (5.7)	
Syndrome or genetic abnormality			0.24
No	479 (84.8)	480 (88.2)	
Yes	63 (11.2)	46 (8.5)	
Suspected	23 (4.1)	18 (3.3)	
Mechanical ventilatory support on PICU admission	501 (88.7)	479 (87.9)	0.69
Inotrope or vasopressor medication on PICU admission	234 (41.4)	221 (40.6)	0.77
Mechanical hemodynamic support on PICU admission	17 (3.0)	22 (4.0)	0.35

PELOD = Paediatric Logistic Organ Dysfunction, range from 0 to 71, with higher scores indicating more severe illness; PIM2 = Paediatric Index of Mortality 2, with higher scores indicating a higher risk of mortality; PN = parenteral nutrition; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth, range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[a]Well-undernourished defined as weight-for-age Z-score ≥2 if <1 year, or BMI-for-age Z-score ≥2 if ≥1 year.[131,143]

[b]<1 year: weight-for-age Z-score, ≥1 year: BMI-for-age Z-score.[131,143]

[c]Based on PIM2 score =([exp (PIM2)]/[1+exp (PIM2)])*100%.

Table S6: Outcomes of Late-PN versus Early-PN in well-nourished children

Outcome	Early-PN (n=565)	Late-PN (n=545)	P-value	Adjusted OR or HR (95% CI)[a]	P-value[a]
Primary endpoint					
New infections	102 (18.1)	59 (10.8)	0.001	0.53 (0.37-0.77)[b]	0.001
Duration of PICU stay — median (IQR), d	4 (2-8)	3 (2-7)	0.03	1.16 (1.03-1.31)	0.02
Secondary safety endpoint					
Death during first week	19 (3.4)	14 (2.6)	0.44	0.55 (0.22-1.40)[b]	0.21
Death during PICU stay	30 (5.3)	23 (4.2)	0.40	0.69 (0.34-1.37)[b]	0.29
Death during hospital stay	38 (6.7)	27 (5.0)	0.21	0.62 (0.34-1.14)[b]	0.12
90-day mortality	39 (6.9)	26 (4.8)	0.13	0.56 (0.30-1.05)[b]	0.07
Hypoglycaemia (blood glucose <40 mg/dl) during first week after randomisation	22 (3.9)	45 (8.3)	0.002	3.19 (1.77-5.73)[b]	<0.001
Weight Z-score deterioration	107 (59.1)	108 (57.8)	0.79	0.96 (0.63-1.47)[b]	0.85
Secondary efficacy endpoint					
Duration of mechanical ventilatory support – median (IQR), d	2 (1-6)	2 (1-4)	0.07	0.11 (0.98-1.25)	0.11
Duration of hospital stay – median (IQR), d	11 (6-22)	10-6-21)	0.09	1.12 (0.99-1.26)	0.08

PELOD = Paediatric Logistic Organ Dysfunction, range from 0 to 71, with higher scores indicating more severe illness; PIM2 = Paediatric Index of Mortality 2, with higher scores indicating a higher risk of mortality; PICU = paediatric intensive care unit; PN = parenteral nutrition; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth, range from 0 to 5, with a score of 0 indicating low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[a]Odds ratio (OR) or Hazard ratio (HR), adjusted for baseline risk factors center, age, diagnosis group, PELOD score, PIM2 score, and STRONGkids category, with corresponding 95% Confidence Interval (CI).

[b]These values are adjusted ORs, the other values are adjusted HRs.

Chapter 5

Effect of Late versus Early Initiation of Parenteral Nutrition on Weight Deterioration during PICU Stay: Secondary Analysis of the PEPaNIC Randomised Controlled Trial

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ABSTRACT

Background and aims

Critically ill children are at increased risk of weight deterioration in the paediatric intensive care unit (PICU). Whether early initiation of parenteral nutrition (PN) prevents weight deterioration is unknown. The aims of this study were to assess the effect of withholding supplemental PN during the first week on weight Z-score change in PICU and to evaluate the association between weight Z-score change in the PICU and clinical outcomes.

Methods

This is a secondary analysis of the Paediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC) randomised controlled trial (n=1440), which focused on the subgroup of patients with longitudinal weight Z-scores available on admission and on the last day in PICU. Patients were randomly allocated to initiation of supplemental PN after one week (Late-PN) or within 24 hours (Early-PN) when enteral nutrition was insufficient. The effect of Late-PN versus Early-PN on the change in weight Z-score was investigated, adjusted for risk factors. Moreover, the association between weight Z-score change and clinical outcomes was explored, adjusted for risk factors.

Results

Longitudinal weight Z-scores were available for 470 patients. Enteral nutrition intake was equal in the Early-PN and Late-PN group. Less weight Z-score deterioration during PICU stay was associated with a lower risk of new infections (adjusted OR per Z-score increase 0.72 [0.55-0.96], p=0.02), and with a higher likelihood of an earlier discharge from PICU alive (adjusted HR per Z-score increase 1.22 [1.10-1.37], p<0.001). During PICU-stay, the change in weight Z-score did not differ among both groups (Late-PN median 0.00 [-0.34-0.12] vs Early-PN median -0.03 [-0.48-0.01], adjusted β=0.10 [-0.05-0.25], p=0.18).

Conclusions

Weight deterioration during the PICU stay was associated with worse clinical outcomes. Withholding supplemental PN during the first week did not aggravate weight Z-score deterioration during PICU stay.

INTRODUCTION

Critically ill children admitted to the paediatric intensive care unit (PICU) are at increased risk for deterioration of their nutritional status.[4,5,7,42,156] Although increased nutritional intake is associated with improved nutritional status, the role of parenteral nutrition (PN) is unknown. Recently, the "Paediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC)" randomised controlled trial showed that withholding supplemental PN during the first week of intensive care (Late-PN) resulted in, among others, fewer new infections and a reduced duration of PICU stay as compared with initiating PN at day 1 (Early-PN).[18] Since the nutritional intake was lower in the Late-PN group because of delaying PN, this strategy might have impacted the nutritional status of these children. Therefore, we aimed to investigate the effect of withholding supplemental PN for 1 week on the change in weight Z-score during PICU stay as compared with early initiation of PN, and whether weight Z-score deterioration during PICU stay is associated with worse clinical outcome.

Materials and Methods

Study design

This is a secondary analysis of the PEPaNIC randomised controlled trial in a subgroup of children with anthropometric measurements available on admission and on the last day in PICU. The trial was conducted at the University Hospitals Leuven, Belgium; Erasmus MC–Sophia Children's Hospital, Rotterdam, the Netherlands; and Stollery Children's Hospital, Edmonton, AB, Canada between 2012 and 2015.The full study protocol has been reported previously, trial registration number is NCT01536275 (clinicaltrials.gov).[18,129] Briefly, 1440 critically ill children (term newborns to 17 years old) were randomly assigned 1:1 to Late-PN or Early-PN, if enteral nutrition (EN) was <80% of target. Early administration of PN was standard of care at that time in the participating hospitals. Patients with a low risk of malnutrition on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) were excluded. Patients in the Late-PN group received a dextrose 5%/saline infusion to match the administered fluid of those in the Early-PN group. Initiation and incline of EN and intravenous administration of micronutrients were similar in both groups. After the first week, patients in both groups received supplemental PN if EN was <80% of target. The institutional ethical review boards of the participating centres approved the study. Written informed consent was obtained from the parents or legal guardians.

Definitions and outcomes

Change in weight Z-score was calculated from admission to the last day in PICU. Weight was measured to the nearest 0.01 kg using calibrated scales. The broad age range of our patients did not allow us to use the same measure of weight Z-score for all children. Therefore, weight Z-score was defined as weight-for-age Z-score[157] in children <1 year old and BMI-for-age Z-score[157] in

children ≥1 year old, as was done previously.[119] In neonates, birthweight-for-gestational age Z-scores[130] were used until the age of 7 days to account for physiologic weight loss during the first week of life. Clinical outcomes were the risk of new infections during PICU stay, and the likelihood of an earlier discharge from PICU alive, with the duration of PICU stay censored at 90 days, and the duration of PICU stay of non-survivors set beyond that of all survivors at 91 days, to account for mortality as a competing risk. Discharge from PICU was a priori defined as ready for discharge from PICU (i.e. no longer in need, or at risk, of vital organ support).

Statistical analysis

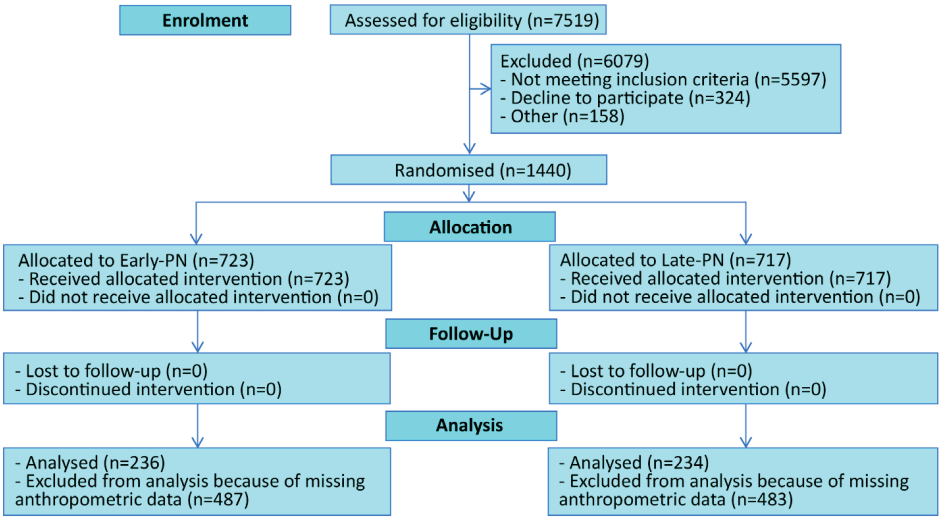
Variables are reported as proportions, mean (±SD) or median (IQR) as appropriate. Proportions were analysed univariably using χ^2 test, means with *t*-test and medians with Mann-Whitney test. The effect of Late PN on change in weight Z-score was analysed using linear regression, adjusted for the baseline risk factors centre, age, diagnosis group (aggregated to 4 groups based on stratification groups), STRONGkids category, Paediatric Logistic Organ Dysfunction (PELOD) score, Paediatric Index of Mortality 2 (PIM2) score, and weight Z-score on admission. The associations between change in weight Z-score and the risk of new infections or the likelihood of earlier discharge from PICU alive were analysed using logistic regression and Cox proportional hazard analyses, respectively, adjusted for the baseline risk factors mentioned above. Weight was measured to the nearest 0.01 kg using calibrated scales. Beta values (β), odds ratios (OR) and hazard ratios (HR) with corresponding 95% confidence intervals were calculated.

P-values ≤0.05 were considered statistically significant. All analyses were performed with IBM SPSS Statistics version 21. Z-scores were calculated with use of Growth Analyzer Research Calculation Tool version 4, and Fenton 2013 Preterm Growth Chart version 6.

RESULTS

Anthropometric measurements on admission and at the last day in PICU were available for 470 Dutch children (Figure 1), equally divided between the randomisation groups and with similar baseline characteristics in the Late-PN and Early-PN groups (Table 1).

Figure 1: CONSORT flow diagram



PN = parenteral nutrition.

The total caloric intake during the first week differed significantly between the treatment groups due to differences in PN, whereas enteral intake was similar between the groups, according to the trial protocol (Table 2). Patients who were included in the analyses differed from those not included: they were younger, had a higher proportion of children with a high STRONGkids score, a lower PELOD score, a higher proportion of emergency admission, comprised more respiratory diagnoses and less cardiac surgery, and a lower proportion of inotrope or vasopressor medication on admission (Table 1). There were no significant differences between the Dutch children who were included and those excluded from the analyses (data not shown), which indicates that the observed baseline differences could be attributed to selection of centre rather than selection bias.

Table 1: Baseline characteristics of total PEPaNIC population and children with anthropometric measurements available on admission and PICU discharge

Characteristic	Total PEPaNIC population			Included in analyses		
	Not included in analyses (n=970)	Included in analyses (n=470)	P-value	Early-PN (n=236)	Late-PN (n=234)	P-value
Male – No. (%)	560 (57.7)	270 (57.4)	0.92	132 (55.9)	138 (58.9)	0.52
Age at randomisation - median years (IQR)	2.03 (0.40-7.19)	0.42 (0.04-3.92)	<0.001	0.46 (0.06-4.21)	0.34 (0.03-3.18)	0.45
Neonate <28 days at randomisation – No. (%)	73 (7.5)	136 (28.9)	<0.001	62 (26.3)	74 (31.6)	0.20
High STRONGkids category – No. (%)	55 (5.7)	97 (20.6)	<0.001	54 (22.9)	43 (18.4)	0.26
Weight Z-score – mean (SD)[a]	-0.63 (1.91)	-072 (1.81)	0.39	-0.72 (1.89)	-0.72 (1.73)	0.97
Undernourished upon admission – No. (%)[b]	187 (20.2)	103 (21.9)	0.45	55 (23.3)	48 (20.5)	0.50
PELOD score – median (IQR)	23 (20-32)	12 (2-13)	<0.001	12 (2-13)	12 (2-21)	0.27
PIM2 score – mean (SD)	-2.53 (1.77)	-2.44 (1.70)	0.34	-2.39 (1.69)	-2.48 (1.72)	0.56
Emergency admission – No. (%)	430 (44.3)	353 (75.1)	<0.001	176 (74.6)	177 (75.6)	0.83
Diagnostic group – No. (%)			<0.001			0.93
Surgical						
Abdominal	30 (3.1)	84 (17.9)		37 (15.7)	47 (20.1)	
Burns	8 (0.8)	2 (0.4)		2 (0.8)	0 (0.0)	
Cardiac	465 (47.9)	82 (17.4)		40 (16.9)	42 (17.9)	
Neurologic	79 (8.1)	37 (7.9)		20 (8.5)	17 (7.3)	
Thoracic	39 (4.0)	22 (4.7)		13 (5.5)	9 (3.8)	
Transplant	13 (1.3)	11 (2.3)		5 (2.1)	6 (2.6)	
Trauma/orthopedic	50 (5.2)	3 (0.6)		2 (0.8)	1 (0.4)	
Other	26 (2.7)	22 (4.7)		9 (3.8)	13 (5.6)	
Medical						
Cardiac	33 (3.4)	28 (6.0)		15 (6.3)	13 (5.6)	
Gastro-intestinal/hepatic	4 (0.4)	2 (0.4)		1 (0.4)	1 (0.4)	
Hematologic/oncologic	6 (0.6)	9 (1.9)		5 (2.1)	4 (1.7)	
Neurologic	57 (5.9)	46 (9.8)		22 (9.3)	24 (10.3)	
Renal	1 (0.1)	1 (0.2)		1 (0.4)	0 (0.0)	
Respiratory	99 (10.2)	96 (20.4)		51 (21.6)	45 (19.2)	
Other	60 (6.2)	35 (5.3)		13 (5.5)	12 (5.1)	

Table 1 continued

Mechanical ventilation on admission – No. (%)	850 (87.6)	411 (87.4)	0.92	208 (88.1)	203 (86.8)	0.68
Inotrope or vasopressor medication on admission – No. (%)	435 (44.8)	157 (33.4)	<0.001	79 (33.5)	78 (33.3)	1.00
Mechanical hemodynamic support on admission – No. (%)	27 (2.8)	17 (3.6)	0.39	6 (2.5)	11 (4.7)	0.23

PELOD = Paediatric Logistic Organ Dysfunction; PICU = paediatric intensive care unit; PIM2 = Paediatric Index of Mortality 2; PN = parenteral nutrition; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth.

[a]≤7 days: birthweight-for-gestational age Z-score, 8 days to 1 year: weight-for-age Z-score, ≥1 year: BMI-for-age Z-score.

[b]Acutely undernourished was defined as a Z-score <-2.

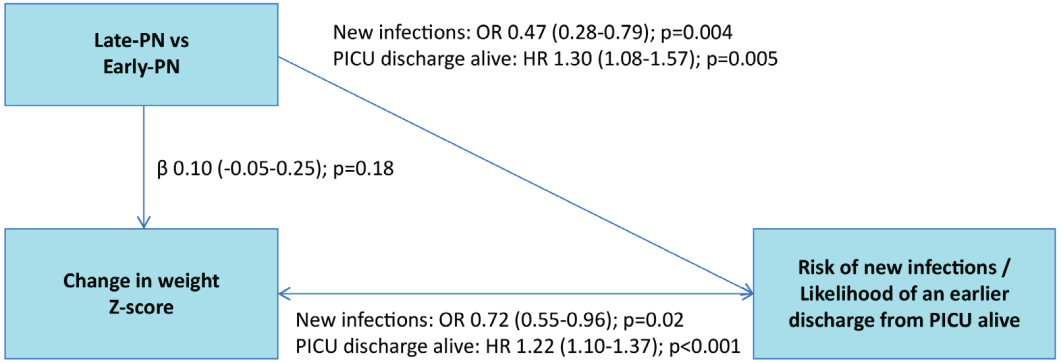
Table 2: Caloric intake for the first seven days in PICU

	n		Total intake (kcal/kg)		Enteral intake (kcal/kg)		Parenteral intake (kcal/kg)	
Day	Early-PN	Late-PN	Early-PN	Late-PN	Early-PN	Late-PN	Early-PN	Late-PN
1	236	234	12.8 (6.9-21.7)	6.3 (3.0-10.6)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	12.4 (6.7-18.7)	5.9 (2.7-9.3)
2	215	212	44.8 (30.9-63.0)	13.0 (8.3-33.0)	0.0 (0.0-21.8)	2.3 (0.0-24.0)	31.1 (14.0-47.7)	7.6 (3.3-11.6)
3	175	176	63.3 (42.4-80.2)	25.7 (11.8-55.5)	16.2 (0.0-50.1)	14.3 (0.0-51.4)	29.5 (7.5-53.7)	5.5 (2.0-11.2)
4	159	143	68.8 (42.2-87.3)	33.9 (13.1-73.3)	32.1 (4.9-68.4)	25.7 (0.0-69.6)	17.8 (1.3-47.2)	4.3 (1.5-10.5)
5	140	114	69.8 (42.6-95.4)	42.1 (17.2-85.7)	34.5 (3.4-77.3)	34.2 (5.4-80.9)	11.4 (0.8-38.4)	3.6 (0.7-10.1)
6	123	94	71.7 (41.0-98.8)	50.2 (18.9-85.6)	36.0 (2.8-81.0)	43.8 (9.6-85.1)	6.6 (0.2-35.9)	2.5 (0.6-7.6)
7	109	78	77.0 (45.8-104.6)	55.4 (21.6-88.0)	45.2 (8.6-82.2)	48.3 (12.4-84.2)	4.9 (0.2-39.8)	2.5 (0.4-6.4)

Data represent medians and interquartile ranges. PICU = paediatric intensive care unit; PN = parenteral nutrition.

All total intakes and parenteral intakes of energy were significantly different for patients in the Early-PN and Late-PN groups. while no significant differences were observed for enteral intakes. N indicates the number of patients still in PICU on the respective days.

Figure 2: Schematic overview of relations tested



All relations were tested separately and independent of each other. PN = parenteral nutrition.

In the children included in this secondary analyses, Late-PN reduced the risk of new infections compared to Early-PN (Late-PN 12.4% vs Early-PN 21.6%, p=0.01; adjusted OR 0.47 [0.28-0.79], p=0.004; Figure 2). The duration of PICU stay was significantly shorter in the Late-PN group (median 4 days [3-9]) than in the Early-PN group (median 6 days [2-13]; p=0.04). Furthermore, the likelihood of an earlier discharge from PICU alive was higher among children in the Late-PN group than those in the Early-PN group (adjusted HR 1.30 [1.08-1.57], p=0.005; Figure 2).

Less weight Z-score deterioration during PICU stay was associated with a lower risk of new infections (adjusted OR per Z-score increase 0.72 [0.55-0.96], p=0.02; Table 3, Figure 2), and with a higher likelihood of an earlier discharge from PICU alive (adjusted HR per Z-score increase 1.22 [1.10-1.37], p<0.001; Table 4; Figure 2).The median change in weight Z-score from admission to the last day in PICU was not significantly different between the treatment groups (Late-PN median 0.00 [-0.34-0.12] vs Early-PN median -0.03 [-0.48-0.01], univariable p=0.19; adjusted β 0.10 [-0.05-0.25], p=0.18, Figure 2).

Table 3: Association of the change in weight Z-score with the risk of acquiring new infections in PICU

Variable	Univariable			Multivariable		
	OR	95% CI	P-value	OR	95% CI	P-value
Change in weight Z-score	0.75	0.57-0.99	0.04	0.72	0.55-0.96	0.02
PELOD score				1.05	1.02-0.08	0.003
PIM2 score				1.16	0.96-1.40	0.12
STRONGkids category				1.59	0.86-2.92	0.14
Age				1.03	0.98-1.08	0.25
Diagnosis group Cardiac surgery (reference)				-	-	-
Diagnosis group Surgery other				0.67	0.33-1.35	0.26
Diagnosis group Medical Neurologic				0.24	0.07-0.83	0.02
Diagnosis group Medical other				0.65	0.31-1.34	0.24
Weight Z-score on admission				0.95	0.81-1.11	0.50

New infections was coded as: 0 = no new infection, 1 = new infection.

PELOD = Paediatric Logistic Organ Dysfunction; PICU = paediatric intensive care unit; PIM2 = Paediatric Index of Mortality 2; PN = parenteral nutrition; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth.

Since the duration of PICU stay differed between the treatment groups, we additionally investigated the average change in weight Z-score per day in PICU, which was a median of 0.00 (-0.06-0.01) in the Late-PN group and 0.00 (-0.05-0.00) in the Early-PN group (univariable p=0.50; adjusted β 0.03 [-0.04-0.10], p=0.35). Change in weight Z-score within children aged <1 year was not different between the Late-PN and Early-PN groups (Late-PN median -0.01 [-0.39;0.08] vs Early-PN median -0.10 [-0.53;0.08], univariable p=0.37; adjusted β 0.04 [-0.13;0.20), p=0.68]. Within children aged ≥1 year, we also did not find a difference in change in weight Z-score between Late-PN and Early-PN (Late-PN median -0.001 [-0.26;0.20]

vs Early-PN median -0.002 [-0.33;0.003], univariable p=0.28; adjusted β 0.19 [-0.07;0.46], p=0.16).

Table 4: Association of the change in weight Z-score with the likelihood of an earlier discharge from PICU alive

Variable	Univariable			Multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value
Change in weight Z-score	1.12	1.01-1.24	0.03	1.22	1.10-1.37	<0.001
PELOD score				0.98	0.97-1.00	0.007
PIM2 score				0.86	0.80-0.92	<0.001
STRONGkids category				0.79	0.62-1.00	0.05
Age				0.98	0.96-1.00	0.06
Diagnosis group Cardiac surgery (reference)				-	-	-
Diagnosis group Surgery other				0.93	0.71-1.22	0.60
Diagnosis group Medical Neurologic				1.17	0.81-1.69	0.42
Diagnosis group Medical other				0.78	0.59-1.04	0.09
Weight Z-score on admission				1.08	1.01-1.14	0.02

PELOD = Paediatric Logistic Organ Dysfunction; PICU = paediatric intensive care unit; PIM2 = Paediatric Index of Mortality 2; PN = parenteral nutrition; STRONGkids = Screening Tool for Risk on Nutritional Status and Growth.

DISCUSSION

In this secondary analysis of the PEPaNIC trial, we found in the subgroup of children with available longitudinal anthropometric data that less weight Z-score deterioration during PICU stay was associated with a lower risk of new infections and with a higher likelihood of an earlier discharge from PICU alive. However, these associations should be interpreted with caution, as cause and consequence within these associations remains unclear (i.e. acquiring a new infection might lead to weight Z-score deterioration). Furthermore, withholding supplemental PN during the first week, and thus accepting low macronutrient intakes, did not affect weight Z-score during PICU stay compared to early supplemental PN. The effect of supplemental PN on the change in weight has not been investigated with a randomised design before. In several observational studies, less nutritional intake during the first 2 weeks or during the entire PICU or hospital admission was associated with deterioration of the child's nutritional status.[4,6,7] However, due to the observational design of these studies, their results could be confounded. Moreover, in these studies, the total caloric intake from EN and PN was investigated. In our study, we found that withholding supplemental PN did not aggravate weight Z-score deterioration while it decreased the risk of new infections and reduced the duration of PICU stay.

These results question the value of weight Z-score change to guide the effect of nutritional therapy in the acute phase of critical illness. Possibly, weight Z-score deterioration could be considered an expression of illness severity. Consensus statements on diagnosing

malnutrition recognise disease burden/inflammation to contribute to illness-related malnutrition, although the precise role of inflammation is not yet clear.[158,159] In case of severe inflammation such as critical illness, an adaptive housekeeping process called autophagy is essential to control cell damage.[160] Early administration of nutrients, in particular of amino acids, was found to suppress autophagy.[132] In critically ill adults, a fasting response evoked by withholding supplemental PN resulted in more efficient activation of autophagy in muscles and reduced muscle weakness.[55] Hence, in critically ill patients in whom severe inflammation is present, increased artificial nutritional support might not be able to prevent nutritional status deterioration. Instead, reduction of cell damage during the acute phase of illness, even if a reduction of nutritional intake is necessary to achieve this, might contribute to optimal muscle and lean body mass preservation.

Body weight might be distorted by oedema and fluid retention, and is therefore difficult to measure reliably in the PICU setting, which warrants caution when interpreting these results. However, such inaccuracies in weight measurements were likely similar in both groups of our study, due to the randomised design and equal fluid administration. It would have been interesting to investigate changes in body composition or muscle tissue between the two groups. Possible measurements of body composition could be dual X-ray absorptiometry (DXA), bioelectrical impedance (BIA/BIS) or plethysmography. However, all of these measurements have some important disadvantages in critically ill children, as the children have to be stable enough to be transported, and in case of plethysmography should be awake and able to sit.[161,162] Despite its limitations, BIA/BIS might be a promising technique for future research. Phase angle measurements derived from BIS have recently been associated with nutritional status and clinical outcomes in critically ill children.[46,163] Currently, the effect of nutritional therapies on change in phase angle during PICU stay in relation with clinical outcomes is unknown. Other measurements to estimate body composition could be mid-upper arm circumference or skinfold thickness, which are both less influenced by oedema than weight, and easy to obtain at the bedside.[164] Information on muscle wasting and structure can be derived from muscle biopsies or imaging. In the EPaNIC study in critically ill adults, muscle biopsies taken at day 8 showed that Late-PN allowed more efficient activation of autophagic quality control.[55] Moreover, in participants of the EPaNIC study, CT images made at day 2 and day 9 showed that withholding supplemental PN during the first week of critical illness did not affect muscle wasting but improved the quality of the muscle, reflected by the decreased amount of adipose tissue within the muscle compartments.[57] Whether these observations can also be applied to critically ill children in different age categories is unknown. In critically ill children, it is difficult to detect an altered muscle structure. The reliability and accuracy of ultrasonography to evaluate muscle wasting in critically ill children is questionable.[49,165]

There are additional limitations to our study that need to be addressed. First, as this study comprised a subgroup, there may be a selection bias. However, the observed baseline differences could be attributed to selection of centre instead of selection bias. Furthermore, the Late-PN and Early-PN groups were comparable at baseline. Therefore, we feel that the

results regarding the effect of Late-PN versus Early-PN on the change in weight Z-score are reliable. Nevertheless, caution is warranted when generalising these results. Second, in this study, we presented short-term outcomes. Recently, the 2 years follow-up of the PEPaNIC patients showed no differences in weight, height, body mass index and head circumference Z-scores between the Late-PN and Early-PN groups.[124] Thus, also in the long-term, there seem to be no repercussions on growth when PN is withheld during the first week of paediatric critical illness.[124]

CONCLUSIONS

In a large heterogeneous PICU population, weight deterioration during PICU stay was associated with worse clinical outcomes. Withholding supplemental PN during the first week of critical illness did not aggravate weight Z-score deterioration during PICU-stay.

Chapter 6

Long-Term Developmental Effects of Withholding Parenteral Nutrition for 1 Week in the Paediatric Intensive Care Unit: a 2-Year Follow-Up of the PEPaNIC International, Randomised, Controlled Trial

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ABSTRACT

Background

The Paediatric Early versus Late Parenteral Nutrition in Critical Illness (PEPaNIC) multicentre, randomised, controlled trial showed that compared with early parenteral nutrition (Early-PN), withholding supplemental parenteral nutrition for 1 week in the paediatric intensive care unit (PICU; Late-PN) reduced infections and accelerated recovery from critical illness in children. We aimed to investigate the long-term impact on physical and neurocognitive development of early versus late parenteral nutrition (PN).

Methods

In this preplanned 2-year follow-up study, all patients included in the PEPaNIC trial (which was done in University Hospitals Leuven, Belgium; Erasmus MC–Sophia Children's Hospital, Rotterdam, the Netherlands; and Stollery Children's Hospital, Edmonton, AB, Canada) were approached for possible assessment of physical and neurocognitive development compared with healthy children who were matched for age and sex, and who had never been admitted to a neonatal ICU or a PICU. Assessed outcomes comprised anthropometric data; health status; parent/caregiver-reported executive functions, and emotional and behavioural problems; and tests for intelligence, visual-motor integration, alertness, motor coordination, inhibitory control, cognitive flexibility, and memory. To address partial responses among the children tested, we did multiple data imputation by chained equations before univariable and multivariable linear and logistic regression analyses adjusted for risk factors. This trial is registered with ClinicalTrials.gov, number NCT01536275.

Findings

At the 2-years follow-up, 60 (8%) of 717 children who received Late-PN and 63 (9%) of 723 children who received Early-PN had died (p=0.81). 68 (9%) of 717 children who received Late-PN and 91 (13%) of 723 children who received Early-PN were too disabled for neurocognitive assessment (p=0.059), and 786 patients (395 assigned to Late-PN and 391 assigned to Early-PN) consented for testing. 786 patients and 405 healthy control children underwent long-term outcomes testing between August 4, 2014, and January 19, 2018, and were included in the imputation model for subsequent multivariable analyses. Late-PN did not adversely affect anthropometric data, health status, or neurological functioning, and improved parent/caregiver-reported executive functioning (Late-PN vs Early-PN β estimate –2.258, 95% CI –4.012 to –0.504; p=0.011), more specifically inhibition (–3.422, –5.171 to –1.673; p=0.0001), working memory (–2.016, –3.761 to –0.270; p=0.023), and meta-cognition (–1.957, –3.694 to –0.220; p=0.027). Externalising behavioural problems (β estimate –1.715, 95% CI –3.325 to –0.106; p=0.036) and visual-motor integration (0.468, 0.087 to 0.850; p=0.016) were also improved in the Late-PN group compared with the Early-PN group. After Bonferroni correction for multiple comparisons, the effect on inhibitory control remained significant (p=0.0001).

Interpretation

Withholding early PN for 1 week in the PICU did not negatively affect survival, anthropometrics, health status, and neurocognitive development, and improved inhibitory control 2 years after PICU admission.

INTRODUCTION

The Paediatric Early versus Late Parenteral Nutrition in Critical Illness (PEPaNIC) multicentre, randomised, controlled trial revealed that withholding parenteral nutrition (PN) for up to 1 week in the paediatric intensive care unit (PICU), when enteral nutrition (EN) was insufficient, was clinically superior to providing full nutrition up to caloric targets with supplemental PN.[18] Indeed, not giving PN during the first week in PICU and thus, in most patients, accepting low caloric and macronutrient intake reduced the incidence of new infections and accelerated recovery.[18] Despite these short-term clinical benefits, concerns have been raised about potential adverse long-term consequences of low caloric and macronutrient intake for the patients' length, bodyweight, head circumference, health status and neurocognitive development.[75,166] To evaluate long-term value for patients, patient-reported outcomes or rather, in case of children, parent/caregiver-reported outcomes should also be investigated.[167] Any such adverse patient-centred long-term consequences would discourage withholding PN early in the course of paediatric critical illness. Children who have been treated in the PICU tend to have adverse long-term developmental and neurocognitive outcomes.[168] In view of the potential benefits of fasting-induced responses for removal of cell damage and prevention of neurodegeneration,[169,170] we hypothesised that withholding PN early during the course of critical illness in children could also bring about beneficial effects in the long term, in particular for neurocognitive development.

We aimed to investigate whether withholding supplemental PN during the first week in PICU, rather than giving PN to reach nutritional targets as soon as possible, while adequately providing micronutrients, has an impact on survival, health status, and anthropometrics, clinically assessed neurological function, and parent/caregiver-reported and clinically tested neurocognitive outcomes at the 2-year follow-up, compared with matched healthy children.

METHODS

Study design and participants

This study is the preplanned 2-year follow-up of the PEPaNIC trial, in which 1440 critically ill children admitted to the participating PICUs (University Hospitals Leuven, Belgium; Erasmus-MC Sophia Children's Hospital, Rotterdam, Netherlands; Stollery Children's Hospital, Edmonton, AB, Canada) had been enrolled between 2012 and 2015. The full study protocol and acute outcome results have been published.[18,129]

Parents or legal guardians had provided written informed consent on admission to the PICU to contact them for long-term follow-up testing of their child. Survival status was determined by assessment of hospital notes, national registers, or contact with the general practitioner or referring paediatrician. All PICU survivors and their parents or caregivers were first sent a standardised patient information letter. Subsequently, they were contacted by phone to obtain consent for scheduling an appointment for the medical and neurocognitive assessment. Participating patients (Appendix) were assessed either at the hospital or at home;

the latter was offered whenever parents or caregivers considered the burden of coming to the hospital too high. Neonates and infants enrolled in the PEPaNIC trial were assessed at the age of 2.5 years because the youngest appropriate age for parent/caregiver-reported executive functioning (with the Behaviour Rating Inventory of Executive Function [BRIEF] and a general intelligence test, Wechsler Preschool and Primary Scale of Intelligence [WPPSI]) is 2.5 years.

405 healthy control children were recruited for a medical and neurocognitive assessment similar to that of the PEPaNIC patients. These children were demographically matched to the patients for age and sex. To control as much as possible for genetic, socioeconomic, and environmental background, siblings and relatives of the patients were preferably recruited into this control group besides unrelated children recruited from the same geographical area. Exclusion criteria for the control group were previous admission to a neonatal ICU or a PICU, or hospital admission for at least 7 days with need for an intravenous line, history of suspicious or established inborn chronic metabolic diseases requiring a specific diet, such as diabetes, and history of short bowel syndrome on home PN or other conditions that require home PN.

Written informed consent was obtained from the parents or legal guardians or from the adolescent according to local regulations. The institutional review boards at each participating site approved this follow-up study (ML8052; NL49708.078; Pro00038098). The protocol is available online.

Procedures, randomisation and masking

In the PEPaNIC trial,[18] after having obtained consent, children who were admitted to the PICU were randomly allocated (1:1) to receive Early-PN, which was initiating PN within 24 hours of PICU admission to supplement EN whenever 80% of targeted calories per age and bodyweight categories was not reached, or Late-PN. Late-PN meant that, for up to 1 week, patients received a mixture of glucose 5% and sodium chloride 0.9% without other forms of PN (lipid or protein infusions) being administered, corresponding to no PN in the majority of children. After 1 week, for both groups equally, PN could be administered if necessary. When EN covered 80% or more of calculated targets, supplemental PN was discontinued. Total macronutrient doses administered on each of the first 7 days in PICU are shown in the appendix. EN was initiated early for both groups equally, and all patients received intravenous micronutrients until fully enterally fed.

Outcome assessors were physicians and experienced paediatric psychologists who had not been involved in the management of the patients during their stay in the PICU and who were strictly blinded for the randomised allocation to either Late-PN or Early-PN. Parents had not been masked during the time the child was treated in the PICU and were not actively informed about the initial PEPaNIC study results.

Outcomes

In this 2-year follow-up study, the primary outcomes assessed were growth, physical ability, health status, and clinical, neurological, and neurocognitive outcomes. Death and severe

disability precluding neurocognitive testing were a priori defined as safety endpoints. Neurocognitive testability was determined by screening of the medical file or clinical judgment, before the start of the neurocognitive assessment, by the physician or psychologist and confirmed by the parents or caregivers.

For children who were examined at follow-up, head circumferences, bodyweights, and heights were measured. A clinical neurological examination was done to assess gross neurological abnormalities. A structured interview with the parents or caregivers assessed whether the child had been diagnosed with a somatic or psychiatric illness, or had been admitted to a hospital for medical or surgical reasons during the preceding 2 years for healthy control children and during the 2 years following the index PICU admission for patients.

Validated, internationally recognised questionnaires and clinical tests with adequate normative data were used to score performance for a broad range of neurocognitive functions.[20] Patient-reported outcome questionnaires were completed by parents or caregivers. They reported executive functioning in their child with the BRIEF preschool version for children aged 2.5-5 years or BRIEF for patients aged 6-18 years. Overlapping scales of both questionnaires (inhibition, flexibility, emotional control, working memory, and planning and organisation), the overlapping index (meta-cognition, comprising the scales working memory and planning and organisation), and the total score were reported (T scores, with mean 50 [SD 10]).[171,172] Parents or caregivers completed the Child Behaviour Checklist (CBCL 1.5–5 years or CBCL 6–18 years)[173,174] to assess emotional and behavioural problems. Internalising, externalising, and total problems were analysed (T scores, with mean 50 [SD 10]).[173,174]

Clinical tests were used to evaluate neurocognitive functions. General intellectual ability was assessed with use of age-appropriate versions of the Wechsler intelligence quotient (IQ). WPPSI-III-NL[175] was used for children aged between 2.5 years and 5 years 11 months, the Wechsler Intelligence Scale for Children (WISC-III-NL)[176] was used for children aged between 6 years and 16 years 11 months, and the Wechsler Adult Intelligence Scale (WAIS-IV-NL)[177] for adolescents or young adults who were 17 years or older. For all of these tests, total IQ, verbal IQ, and performance IQ scores (test mean 100 [SD 15]) were computed. The Beery Developmental Test of Visual–Motor Integration[178] was used for children aged 2.5 years and older to assess the ability to integrate visual and motor functions (total scaled score, with test mean 10 [SD 3]). The validated computerised Amsterdam Neuropsychological Tasks (ANT) programme was used to measure attention, motor coordination, and executive functions in children aged 4 years or older.[179] ANT-Baseline Speed was used to evaluate alertness (reaction time and SD), ANT-Tapping to assess motor coordination (number of taps), and Response Organisation Objects to measure inhibitory control and cognitive flexibility (differences in reaction time and in number of errors between tests of increasing demand). Memory was assessed with use of 4 tests from the Children's Memory Scale (CMS) for children aged between 5 years and 16 years 11 months.[180] CMS-Numbers assessed short-term verbal memory span and verbal working memory load (scaled score, with test mean 10 [SD 3]). The CMS-Word Pairs assessed short-term and long-term verbal memory, and recognition; CMS-Picture Locations assessed immediate visual memory; and CMS-Dot Locations assessed

immediate and delayed visual memory (proportion of correct responses, ranging from 0 to 1). The CMS-Learning index represents learning abilities of the child (standard score, with mean 100 [SD 15]). The extended description of the parent/caregiver-reported outcome questionnaires and of the clinical and neuropsychological test battery is available in the appendix.

Statistical analysis

After taking into account estimations for the safety endpoints (death and severe disability precluding neurocognitive testing), we estimated that about 30% of the patients among the critically ill patients who had been included in the PEPaNIC trial and who were alive and testable at the 2-year follow-up would be lost to follow-up, on the basis of earlier experience.[20] We calculated that such a sample size had >80% power to detect, with a certainty of >95%, clinically relevant differences between the 2 randomisation arms, in the same order of magnitude as those we had previously documented with blood glucose control in the PICU.[20] For the healthy control group, we calculated that with a sample size of 405 children, we would be able to detect, with a power of >80% and certainty of >95%, outcome differences between patients and healthy children of the same order of magnitude as those previously documented.[20]

The inability to fully complete any of the neurocognitive tests would introduce bias in univariable analyses of these test results, because this in itself might suggest poor function. Hence, to correctly address partial responses, multiple data imputation by chained equations was required,[181] with use of all available data per individual (Appendix). For tests validated for a specific age range (alertness, motor coordination, inhibitory control and flexibility in children aged 4 years or older, and memory in children who are between 5 and 16 years old), we imputed data within these age ranges only. To avoid bias and instability in this imputation model, the percentage of missing data per variable could not exceed 30%[181] and to minimise loss of statistical power, the number of iterative imputations was set at 31.[181] Comparison of the observed and imputed values and the imputation predictor are shown in the appendix.

To analyse the differences in outcomes between PEPaNIC participants and healthy control children, and to investigate the long-term outcome differences between patients randomly allocated to Late-PN or Early-PN during PICU stay, we did multivariable linear and logistic regression analyses on the 31 imputed datasets with the β estimates or odds ratios reported as pooled results, preceded by a pooled univariable comparison with use of Fisher's exact test, Student's *t* test, or Wilcoxon rank-sum test as appropriate (Appendix). All multivariable analyses were adjusted for the following risk factors: age, centre, race,[182] sex, geographic origin,[182] language, hand preference, history of malignancy, diabetes, a predefined syndrome (Appendix), and the educational and occupational status of parents (Appendix). For the comparison between Late-PN and Early-PN groups, further adjustment was done for diagnosis and severity of illness (with the Paediatric Index of Mortality 3 and paediatric logistic organ dysfunction scores) on PICU admission, risk of malnutrition, and parental smoking behaviour before PICU admission. We calculated p values for interaction between age group

and randomisation to assess whether patients who were infants (aged <1 years) at randomisation behaved differently from older children.

We did explanatory statistical analyses with further adjustment to investigate whether any eventual impact of Late-PN versus Early-PN on the long-term outcomes might have been mediated by its acute effects on new PICU infections and duration of PICU stay, and thus possibly indirectly also number of post-randomisation hypoglycaemic events or the duration of post-randomisation treatments such as mechanical ventilatory support, haemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics, and α2-agonists.

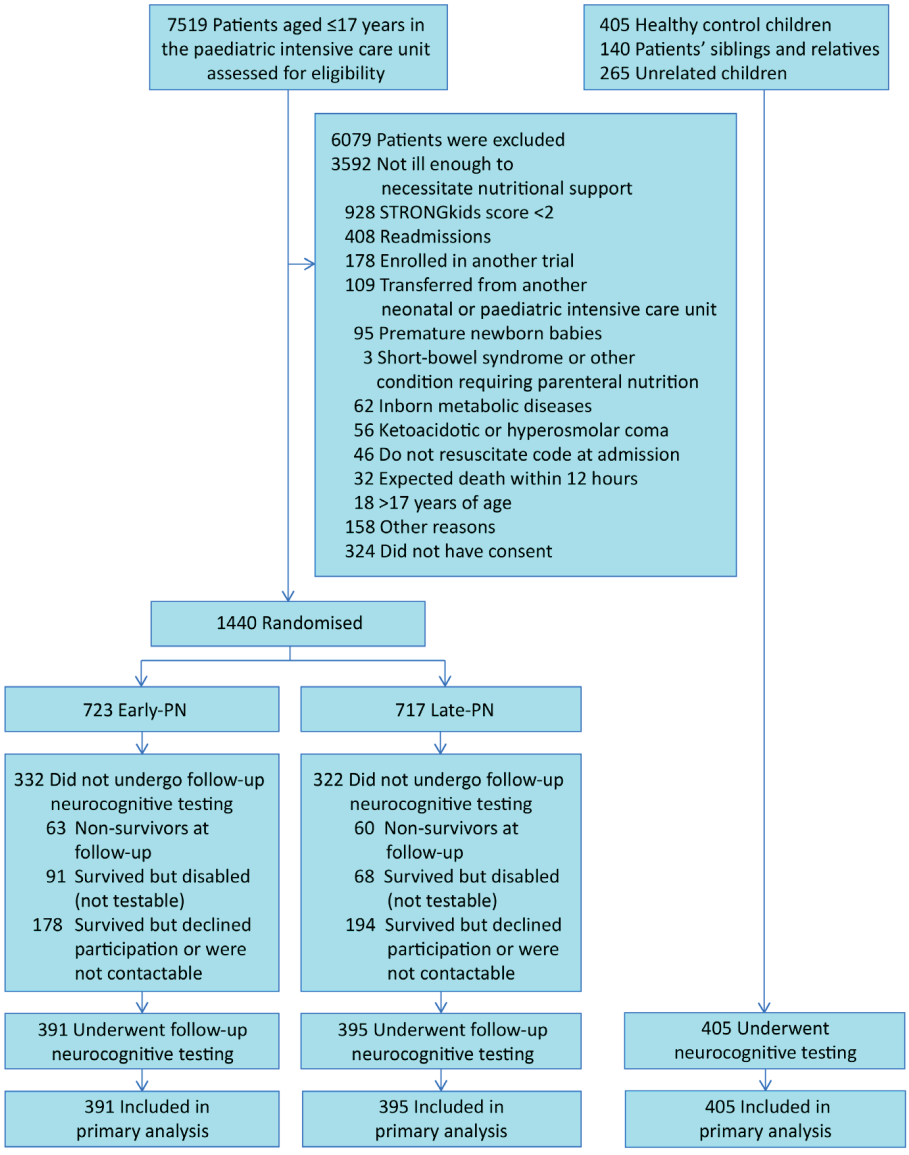
Data are presented as β estimates and odds ratios with 95% CIs, means and SDs, or numbers and proportions, as appropriate.

Statistical analyses were done with R version 3.4.3, MICE version 2.46.0, and JMP version 13.0.0. Two-sided p-values of 0.05 or less were considered statistically significant. Bonferroni corrections for the multiple comparisons (n=45) were done as a sensitivity analysis, which altered the required level of p value for significance to 0.001 or less.

This trial is registered with ClinicalTrials.gov, NCT01536275.

RESULTS

Figure 1: CONSORT flow diagram of the study participants



PN = parenteral nutrition, STRONGkids = Screening Tool for Risk on Nutritional Status and Growth.

Of the total patient population (n=1440), 60 (8%) of 717 children in the Late-PN group and 63 (9%) of 723 children in the Early-PN group had died 2 years after admission to a PICU (p=0.81; Figure 1). 68 (9%) patients in the Late-PN group and 91 (13%) patients in the Early-PN group were identified as too disabled to assess for neurocognitive development (p=0.059). 372 (26%) patients survived, but declined participation or could not be reached. No differences in reasons for loss to follow-up between randomisation groups were observed (p=0.27). 786 patients (395 assigned to Late-PN and 391 assigned to Early-PN) and 405 healthy controls underwent long-term outcome testing between August 4, 2014 and January 19 2018, and were included in the imputation model for subsequent multivariable analyses. Of the healthy control children, 332 (82%) were assessed at the hospital compared with 502 (64%) PEPaNIC children (p<0.001), with similar proportions for the Early-PN 458 (64%) and Late-PN 461 (64%) groups being assessed at the hospital (p=0.79). Demographic and medical characteristics of PEPaNIC participants and healthy control children are shown in Table 1. Patients who were tested at follow-up were overall comparable to the initial PEPaNIC study population (Table 1).

Overall, PEPaNIC participants had worse outcomes at the 2-year follow-up for height, body weight, and head circumference, for health status, clinically assessed neurological functioning, parent/caregiver-reported executive functioning, and emotional and behavioural problems, and for clinical tests for intelligence, visual-motor integration, alertness, and memory than did healthy control children, assessed via univariable and via multivariable comparisons (Table 2; Table 3).

Patients in the Late-PN group and those in the Early-PN group were similar in terms of height, bodyweight, body-mass index, and head circumference, and for health status, and clinically assessed neurological functioning in univariable and multivariable analyses (Table 2, Table 3) However, in the univariable comparisons, patients in the Late-PN group performed better than did those in the Early-PN group on parent/caregiver-reported inhibitory control, working memory, meta-cognition, and overall executive functioning, and on clinical tests for visual-motor integration, verbal-auditory recognition, and for one motor coordination task (synchronous tapping; Table 2). Adjusted for multiple comparisons, the better inhibitory control of patients in the Late-PN group than that of patients in the Early-PN group remained significant (p=0.0001). After multivariable adjustment for risk factors, parents/caregivers of patients in the Late-PN group reported better overall executive functioning than did parents/caregivers of patients in the Early-PN group (β estimate –2.258, 95% CI –4.012 to –0.504; p=0.011), more specifically for inhibition (–3.422, –5.171 to –1.673; p=0.0001), working memory (–2.016, –3.761 to –0.270; p=0.023), and metacognition (–1.957, –3.694 to –0.220; p=0.027; Table 3; Figure 2). Furthermore, patients in the Late-PN group had fewer externalising behavioural problems (–1.715, 95% CI –3.325 to –0.106; p=0.036) as reported by parents/caregivers and scored better on visual-motor integration (0.468, 0.087 to 0.850; p=0.016) than did patients in the Early-PN group (Table 3; Appendix).

Table 1: Demographics of patients and healthy control children, post-randomisation treatments in the PICU, and acute outcomes

	Tested population[a]		Total PEPaNIC population		Tested PEPaNIC population[b]	
	Healthy control children (n=405)	PEPaNIC patients (n=786)	Early-PN (n=723)	Late-PN (n=719)	Early-PN (n=391)	Late-PN (n=395)
Demographic						
Age at 2-year follow-up - years	6.0 (4.7)	5.7 (4.5)	NA	NA	5.7 (4.4)	5.6 (4.5)
Sex						
Female	186 (46%)	331 (42%)	331 (42%)	305 (43%)	161 (41%)	170 (43%)
Male	219 (54%)	455 (58%)	415 (57%)	412 (57%)	230 (59%)	225 (57%)
Known non-white race[c]	33 (8%)	63 (8%)	50 (7%)	33 (5%)	38 (10%)	25 (6%)
Known non-European origin[c]	54 (13%)	152 (19%)	161 (22%)	128 (18%)	88 (23%)	64 (16%)
Known not exclusive Dutch or English language	76 (19%5)	184 (23%)	122 (17%)	106 (15%)	95 (24%)	89 (23%)
Socioeconomic status						
Parent[d] educational level 1	13 (3%)	37 (5%)	NA	NA	12 (3%)	25 (6%)
Parent[d] educational level 1.5	23 (6%)	54 (7%)	NA	NA	28 (7%)	26 (7%)
Parent[d] educational level 2	55 (14%)	184 (23%)	NA	NA	96 (25%)	88 (22%)
Parent[d] educational level 2.5	76 (19%)	131 (17%)	NA	NA	60 (15%)	71 (18%)
Parent[d] educational level 3	215 (53%)	200 (26%)	NA	NA	100 (26%)	100 (25%)
Parent[d] educational level unknown	23 (6%)	180 (23%)	NA	NA	95 (24%)	85 (22%)
Parent[e] occupational level 1	2 (<1%)	10 (1%)	NA	NA	2 (<1%)	8 (2%)
Parent[e] occupational level 1.5	25 (6%)	76 (10%)	NA	NA	33 (8%)	43 (11%)
Parent[e] occupational level 2	47 (12%)	127 (16%)	NA	NA	61 (16%)	66 (17%)
Parent[e] occupational level 2.5	26 (6%)	77 (10%)	NA	NA	44 (11%)	33 (8%)
Parent[e] occupational level 3	83 (21%)	121 (15%)	NA	NA	54 (14%)	67 (17%)
Parent[e] occupational level 3.5	40 (10%)	54 (7%)	NA	NA	32 (8%)	22 (6%)
Parent[e] occupational level 4	116 (29%)	108 (14%)	NA	NA	53 (14%)	55 (14%)
Parent[e] occupational level unknown	66 (16%)	213 (27%)	NA	NA	112 (29%)	101 (26%)

Table 1 continued

	Tested population[a]		Total PEPaNIC population		Tested PEPaNIC population[b]	
Patient characteristic upon PICU admission	**Healthy control children (n=405)**	**PEPaNIC patients (n=786)**	**Early-PN (n=723)**	**Late-PN (n=719)**	**Early-PN (n=391)**	**Late-PN (n=395)**
Infant (age<1y) at randomisation	NA	363 (46%)	328 (45%)	325 (45%)	177 (45%)	186 (47%)
STRONGkids risk level[f]						
Medium	NA	707 (90%)	644 (89%)	644 (90%)	351 (90%)	356 (90%)
High	NA	79 (10%)	79 (11%)	73 (10%)	40 (10%)	39 (10%)
PeLOD score, first 24h in PICU[g]	NA	20.0 (11.6)	19.7 (12.0)	20.1 (12.3)	20.0 (11.6)	20.0 (11.5)
PIM3 score[h]	NA	–3.5 (1.4)	–3.2 (1.6)	–3.2 (1.7)	–3.4 (1.4)	–3.5 (1.3)
PIM3 probability of death, %[h]	NA	6.7 (11.8)	9.4 (15.9)	9.1 (17.4)	6.8 (12.0)	6.5 (11.6)
Diagnostic category						
Surgical: abdominal	NA	70 (9%)	53 (7%)	60 (8%)	34 (9%)	36 (9%)
Surgical: burns	NA	2 (<1%)	5 (<1%)	5 (<1%)	1 (<1%)	1 (<1%)
Surgical: cardiac	NA	339 (43%)	279 (39%)	268 (37%)	173 (44%)	166 (42%)
Surgical: neurosurgery or traumatic brain injury	NA	71 (9%)	63 (9%)	53 (7%)	39 (10%)	32 (8%)
Surgical: thoracic	NA	42 (5%)	34 (5%)	27 (4%)	23 (6%)	19 (5%)
Surgical: transplantation	NA	14 (2%)	7 (1%)	17 (2%)	4 (1%)	10 (3%)
Surgical: orthopaedic surgery or trauma	NA	23 (3%)	28 (4%)	26 (4%)	14 (4%)	9 (2%)
Surgical: other	NA	27 (3%)	21 (3%)	27 (4%)	10 (3%)	17 (4%)
Medical: cardiac	NA	26 (3%)	30 (4%)	31 (4%)	10 (3%)	16 (4%)
Medical: gastrointestinal or hepatic	NA	3 (<1%)	2 (<1%)	4 (<1%)	1 (<1%)	2 (<1%)
Medical: oncologic or haematologic	NA	8 (1%)	8 (1%)	7 (1%)	5 (1%)	3 (<1%)
Medical: neurologic	NA	44 (6%)	51 (7%)	52 (7%)	21 (5%)	23 (6%)
Medical: renal	NA	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Medical: respiratory	NA	83 (11%)	99 (14%)	96 (13%)	38 (10%)	45 (11%)
Medical: other	NA	34 (4%)	42 (6%)	43 (6%)	18 (5%)	16 (4%)
Malignancy	0 (0.0)	42 (5%)	51 (7%)	33 (5%)	26 (7%)	16 (4%)
Diabetes	0 (0.0)	1 (<1%)	3 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Syndrome[i]	5 (1.2)	79 (10%)	123 (17%)	118 (16%)	34 (9%)	45 (11%)
Known parental smoking between birth and PICU admission	NA	149 (19%)	NA	NA	72 (18%)	77 (20%)

Acute effect of randomisation and post-randomisation treatment in PICU						
Duration of stay in the PICU - days	NA	7.4 (15.1)	9.2 (21.3)	6.5 (10.0)	8.4 (18.4)	6.4 (10.8)
Patients who acquired a new infection in PICU	NA	105 (13%)	134 (19%)	77 (11%)	66 (17%)	39 (10%)
Duration of mechanical ventilatory support - days	NA	4.7 (11.0)	6.4 (18.6)	4.4 (7.3)	5.5 (13.9)	3.9 (7.1)
No. of days with hypoglycaemia <40mg/dl - days	NA	0.1 (0.5)	0.1 (0.6)	0.2 (0.6)	0.1 (0.5)	0.2 (0.6)
Duration of antibiotic treatment - days	NA	5.1 (13.4)	6.7 (19.0)	4.6 (8.7)	5.8 (16.4)	4.3 (9.5)
Duration of haemodynamic support - days	NA	2.5 (7.2)	3.0 (7.4)	2.4 (6.2)	2.6 (7.6)	2.3 (6.8)
Duration of treatment with opioids - days	NA	4.7 (8.8)	6.1 (16.5)	4.1 (6.2)	5.4 (10.8)	4.1 (6.2)
Duration of treatment with benzodiazepines - days	NA	4.2 (9.8)	5.4 (16.7)	4.0 (8.8)	4.5 (9.9)	3.9 (9.7)
Duration of treatment with hypnotics - days	NA	1.4 (5.6)	1.8 (6.3)	1.3 (3.1)	1.6 (7.4)	1.2 (2.9)
Duration of treatment with α2-agonists - days	NA	1.0 (6.4)	1.1 (8.7)	1.0 (6.0)	0.9 (5.9)	1.1 (6.8)
Duration of treatment with corticosteroids) - days	NA	1.2 (3.7)	1.6 (4.3)	1.3 (3.9)	1.3 (4.2)	1.0 (3.1)

Data are mean (SD) or n (%). BMI=body mass index; NA=not applicable (values only known when the patients were seen at follow-up, or not applicable for healthy control children); PeLOD = Paediatric Logistic Organ Dysfunction score; PICU = paediatric intensive care unit; PIM3 = Paediatric Index of Mortality 3 score; PN = parenteral nutrition; SEM = standard error of the mean.

[a]708 (59%) of 1191 participating children were tested in Belgium, 463 (39%) in the Netherlands, and 20 (2%) in Canada.

[b]No differences in demographics, allocation to Late or Early-PN, and PICU- or hospital-related primary and secondary study endpoints were observed between the PEPaNIC patients who were tested and those who survived, but declined participation or could not be reached (n=372; all p>0.15).

[c]Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.

[d]The education level is the mean of the paternal and maternal educational level, and calculated on the basis of the 3-point scale (1=low, 2=middle, 3-high; Appendix) subdivisions as made by the Algemene Directie Statistiek (Belgium) and the Centraal Bureau voor de Statistiek (The Netherlands).

[e]The occupation level is the mean of the paternal and maternal occupation level, which is calculated on the basis of the International Isco System 4-point scale for professions (Appendix).

[f]STRONGkids scores range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[g]PeLOD scores range from 0 to 71, with higher scores indicating more severe illness.

[h]PIM3 probability of death, ranging from 0-100% with high percentage indicating a higher probability of death in PICU.

[i]A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Appendix).

For overall executive functioning, inhibition, meta-cognition, and externalising problems as reported by parents/caregivers, patients in the Late-PN group were not different from healthy control children (p values of ≥0.12; Appendix). After further correction for multiple comparisons, the better inhibitory control of patients in the Late-PN group than of those in the Early-PN group remained significant (p=0.0001; Table 3). Sensitivity analyses for the missing-at-random assumption and with imputing worst test scores for the severely disabled and thus non-testable children, as presented in the appendix, further supported the robustness of these results.

The effects of Late-PN versus Early-PN were more pronounced in the subgroup of patients who were infants at randomisation than in older children (interaction p values of ≤0.03): β estimates for Late-PN versus Early-PN among infants for parent/caregiver-reported overall executive functioning (-3.843, 95% CI -6.361 to -1.325; p=0.0029), meta-cognition (-3.749, -6.244 to -1.254; p=0.0034), and working memory (-3.594, -6.052 to -1.135; p=0.0043; Appendix).

The impact of Late-PN versus Early-PN on long-term outcomes did not appear to be mediated by its acute effects on new PICU infections, duration of PICU stay, exposure to hypoglycaemia, or duration of potentially hazardous post-randomisation treatments during the PICU stay (Appendix). The use of benzodiazepines and of corticosteroids was independently associated with poorer outcomes, whereas treatment with α2 agonists was associated with better overall executive functioning and visual-motor integration (Appendix).

DISCUSSION

Two years after inclusion in the PEPaNIC multicentre, randomised, controlled trial, PICU survivors had worse developmental outcomes than did healthy control children. However, no adverse effect of withholding PN during the first week in the PICU could be detected for survival, anthropometrics health status, and neurocognitive development. In fact, omitting Early-PN in the PICU improved parent/caregiver-reported executive functioning 2 years later compared with Early-PN, in particular resulting in a better inhibitory control. Moreover, of the patients who survived, fewer were too disabled to be tested in the Late-PN group than in the Early-PN group.

The long-term legacy of problems in executive functioning, as reported in this Article by parents or caregivers of patients admitted to the PICU, has been described previously, although mostly limited to the results of clinical neurocognitive testing.[20,90]

Table 2: Pooled univariable analyses of the differences assessed at 2-year follow-up between patients and healthy control children and between Late-PN and Early-PN patient groups

	Number (%) of available data per outcome before imputation (n=1191)	Tested populations			Tested PEPaNIC population		
		Healthy control children (n=405)	PEPaNIC patients (n=786)	P-value	Early-PN (n=391)	Late-PN (n=395)	P-value
Height – cm	1126 (95%)	114.6 (27.4)	110.6 (26.5)	0.0018[a]	111.2 (25.9)	109.9 (27.0)	0.16
SD score[b]	1126 (95%)	0.370 (1.1)	-0.066 (1.3)	<0.0001[a]	-0.016 (1.2)	-0.115 (1.4)	0.47
Weight – kg	1135 (96%)	24.6 (16.7)	23.0 (16.2)	0.0020	23.0 (15.2)	23.0 (17.0)	0.20
SD score[b]	1135 (96%)	0.425 (0.9)	0.154 (1.2)	<0.0001	0.187 (1.1)	0.122 (1.1)	0.30
Body-mass index – kg/m^3	1126 (95%)	16.9 (2.7)	17.0 (5.1)	0.27	16.9 (3.1)	17.2 (6.5)	0.51
SD score[b]	1126 (95%)	0.306 (1.0)	0.249 (1.2)	0.043	0.259 (1.2)	0.240 (1.2)	0.61
Head circumference – cm	1060 (89%)	51.5 (2.6)	50.9 (2.8)	<0.0001	51.0 (2.8)	50.8 (2.8)	0.14
SD score[b]	1060 (89%)	0.504 (1.1)	0.107 (1.3)	<0.0001	0.139 (1.3)	0.076 (1.3)	0.35
Diagnosed with a somatic illness	957 (81%)	140 (35%)	507 (65%)	<0.0001	259 (66%)	248 (63%)	0.31
Diagnosed with a psychiatric illness	1160 (98%)	16 (4%)	52 (7%)	<0.0001	30 (8%)	22 (6%)	0.23
Admitted to hospital for a medical or surgical reason	1191 (100%)	72 (18%)	425 (54%)	<0.0001	216 (55%)	209 (53%)	0.51
Clinical neurological evaluation score (range 0-8)[c]	1116 (94%)	0.22 (0.6)	0.71 (1.5)	<0.0001	0.81 (1.6)	0.61 (1.3)	0.096
Executive functioning as reported by parents/caregivers - T-score[c]							
Inhibition	850 (72%)	46.3 (11.5)	49.9 (15.2)	<0.0001	51.4 (14.4)	48.4 (13.2)	<0.0001
Flexibility	851 (72%)	46.7 (11.3)	49.9 (15.3)	<0.0001	50.5 (14.3)	49.4 (13.3)	0.12
Emotional control	851 (72%)	47.7 (11.2)	49.7 (13.5)	0.0052	50.0 (12.7)	49.4 (12.4)	0.34
Working memory	845 (71%)	46.7 (12.1)	51.4 (16.7)	<0.0001	52.3 (15.4)	50.6 (14.1)	0.055
Planning and organisation	847 (72%)	46.9 (11.9)	50.3 (14.7)	0.0001	50.8 (13.8)	49.8 (12.9)	0.18
Meta-cognition index	842 (71%)	46.8 (12.5)	50.2 (15.2)	<0.0001	51.0 (14.1)	49.5 (13.5)	0.059
Total score	841 (71%)	45.9 (11.6)	50.2 (15.4)	<0.0001	51.1 (14.5)	49.3 (13.7)	0.029

Table 2 continued

	Number (%) of available data per outcome before imputation (n=1191)	Tested populations			Tested PEPaNIC population		
		Healthy control children (n=405)	PEPaNIC patients (n=786)	P-value	Early-PN (n=391)	Late-PN (n=395)	P-value
Emotional and behavioural problems as reported by parents/caregivers - T-score[c]							
Internalising problems	1014 (86%)	46.7 (10.7)	51.1 (13.5)	<0.0001	51.4 (13.3)	50.8 (12.5)	0.53
Externalising problems	1014 (86%)	46.8 (10.1)	49.8 (13.2)	<0.0001	50.5 (12.7)	49.1 (12.0)	0.11
Total problems	1014 (86%)	46.1 (10.4)	50.9 (13.2)	<0.0001	51.6 (13.0)	50.2 (12.3)	0.12
Intelligence (range 45-155)[d]							
Total IQ	1066 (90%)	100.7 (13.0)	90.6 (16.5)	<0.0001	90.3 (16.6)	90.9 (15.8)	0.57
Verbal IQ	1052 (89%)	100.8 (14.1)	92.0 (18.2)	<0.0001	91.6 (18.2)	92.4 (17.3)	0.55
Performal IQ	1071 (90%)	100.7 (13.8)	91.5 (16.4)	<0.0001	91.4 (16.7)	91.7 (15.6)	0.54
Visual-motor integration (range 0.9-20)[d]	1097 (93%)	9.6 (2.4)	8.2 (3.5)	<0.0001	8.0 (3.5)	8.5 (2.9)	0.010
Alertness[c, e]							
Reaction time right hand - ms	413 (78%)	480.8 (290.2)	561.1 (700.4)	0.0064	591.4 (581.8)	527.6 (489.9)	0.082
Within-person SD of repeated tests	413 (78%)	219.3 (176.0)	278.8 (715.0)	0.056	296.3 (559.0)	259.5 (510.8)	0.29
Reaction time left hand - ms	418 (79%)	459.7 (239.2)	536.2 (538.1)	0.038	557.1 (460.6)	513.0 (412.5)	0.11
Within-person SD of repeated tests	418 (79%)	217.3 (222.4)	287.4 (542.7)	0.063	196.0 (454.0)	177.8 (401.8)	0.23
Motor coordination (number of taps in 10 s) [d, e]							
Number of right hand taps	433 (82%)	41.4 (16.1)	37.9 (41.1)	0.095	37.2 (32.6)	38.8 (28.8)	0.29
Number of left hand taps	433 (82%)	36.3 (14.4)	34.9 (36.6)	0.30	33.7 (29.1)	36.2 (25.9)	0.19
Number of valid alternating taps	392 (74%)	18.3 (23.2)	18.6 (63.8)	0.35	17.4 (49.4)	20.0 (45.7)	0.36
Number of valid synchronous taps	392 (74%)	23.9 (15.1)	21.9 (35.8)	0.19	20.4 (27.6)	23.5 (26.5)	0.041
Inhibition and flexibility[c, e]							
Difference in reaction time (inhibition) - ms	383 (72%)	234.5 (411.0)	264.2 (1207.6)	0.24	286.5 (937.0)	239.6 (826.2)	0.17
Difference in no of errors (inhibition)	385 (73%)	2.1 (12.7)	4.1 (38.6)	0.053	4.2 (28..5)	4.0 (27.3)	0.73
Difference in reaction time (flexibility) - ms	369 (70%)	427.9 (445.3)	445.8 (1149.2)	0.31	458.7 936.0)	431.6 (782.9)	0.49

Table 2 continued

Difference in numbers of errors (flexibility)	370 (70%)	2.4 (10.8)	4.8 (35.7)	0.067	4.6 (26.8)	5.0 (24.8)	0.64
Memory[d, e]							
Verbal-auditory							
Numbers (range 1-19)							
Memory span (forward)	331 (83%)	10.2 (2.9)	8.6 (5.7)	<0.0001	8.6 (5.0)	8.7 (4.4)	0.66
Working memory (backward)	318 (80%)	10.3 (3.0)	8.7 (4.5)	<0.0001	8.9 (4.3)	8.4 (3.7)	0.38
Word pairs (% of correct responses)							
Learning	287 (72%)	0.50 (0.2)	0.43 (0.8)	0.047	0.42 (0.7)	0.45 (0.5)	0.26
Immediate memory	285 (72%)	0.47 (0.2)	0.33 (0.6)	<0.0001	0.31 (0.5)	0.35 (0.4)	0.13
Delayed memory	282 (71%)	0.40 (0.3)	0.31 (0.8)	0.0059	0.30 (0.7)	0.32 (0.5)	0.43
Recognition	279 (70%)	0.95 (0.2)	0.87 (0.5)	0.0003	0.85 (0.4)	0.89 (0.3)	0.043
Non-verbal, visual-spatial							
Pictures (% of correct responses)	319 (80%)	0.85 (0.1)	0.789 (0.3)	0.0001	0.77 (0.2)	0.79 (0.2)	0.29
Dots (% of correct responses)							
Learning	305 (77%)	0.86 (0.2)	0.78 (0.5)	0.010	0.79 (0.4)	0.78 (0.4)	0.57
Immediate memory	305 (77%)	0.87 (0.2)	0.80 (0.8)	0.058	0.80 (0.6)	0.80 (0.5)	0.70
Delayed memory	299 (75%)	0.87 (0.2)	0.80 (0.8)	0.094	0.79 (0.6)	0.80 (0.5)	0.59
Learning index (range 50-150)	280 (71%)	100.2 (22.5)	92.2 (85.5)	0.025	91.9 (69.2)	92.5 (54.9)	0.50

Results are the combined number (%) and means (SD) from 31 datasets generated by multiple data imputation by chained equations under a missing-at-random assumption for the 786 post-PICU patients and 405 healthy control children. IQ = intelligence quotient; PN = parenteral nutrition.

[a]Statistically significant after Bonferroni correction for multiple comparisons.

[b]Age-specific and sex-specific SD scores were calculated with the use of reference data from the WHO Growth Charts. The mean change in Z-scores from admission to a PICU to 2-year follow-up in the tested PEPaNIC population was 0.073 (SD 0.781) for height, 0.533 (1.101) for bodyweight, and 0.673 (1.393) for body-mass index. The mean change in Z-scores from PICU admission to 2-year follow-up for patients who received Late-PN versus those who received Early-PN in the tested PEPaNIC population was 0.027 (SD 1.899) versus 0.119 (1.656; p=0.84) for height, -0.366 (1.314) versus -0.397 (1.316; p=0.34) for bodyweight, and 0.605 (1.429) versus 0.739 (1.355; p=0.31) for body-mass index.

[c]Higher scores reflect worse performance.

[d]Higher scores reflect better performance.

[e]For alertness, motor coordination, executive functions, applicable imputation was limited to relevant age ranges.

Table 3: Multivariable linear and logistic regression analyses of the differences in the outcomes assessed at 2-year follow-up between patients and healthy control children and between Late-PN and Early-PN patient groups.

	Number (%) of available data per outcome before imputation (n=1191)	Beta-estimate or odds ratio (95% CI) for the comparison patients vs controls, adjusted for risk factors[a]	P-value	Beta-estimate or odds ratio (95% CI) for the comparison Late-PN vs Early-PN, adjusted for risk factors[b]	P-value
Height – cm	1126 (95%)	-1.717 (-2.670;-0.763)	0.0004[c]	-0.538 (-3.358;2.282)	0.70
Weight – kg	1135 (96%)	-0.318 (-1.052;0.417)	0.39	0.278 (-1.639;2.194)	0.77
Body-mass index – kg/m^3	1126 (95%)				
Head circumference – cm	1060 (89%)	-0.461 (-0.701;-0.221)	0.0001[c]	-0.150 (-0.496;0.197)	0.39
Diagnosed with a somatic illness	957 (81%)	2.940 (2.199;3.931)[d]	<0.0001[c]	0.881 (0.625;1.242)[d]	0.74
Diagnosed with a psychiatric illness	1160 (98%)	2.137 (1.104;4.136)[d]	0.024	0.764 (0.403;1.448)[d]	0.40
Admitted to hospital for a medical or surgical reason	1191 (100%)	4.781 (3.485;6.559)[d]	<0.0001[c]	0.867 (0.634;1.186)[d]	0.37
Clinical neurological evaluation score (range 0-8)[e]	1116 (94%)	0.296 (0.154;0.439)	<0.0001[c]	-0.134 (-0.308;0.040)	0.13
Executive functioning as reported by parents/caregivers - T-score[f]					
Inhibition	850 (72%)	2.067 (0.507;3.628)	0.0095	-3.422 (-5.171;-1.673)	0.0001[c]
Flexibility	851 (72%)	1.611 (0.107;3.114)	0.035	-1.146 (-2.841;0.550)	0.18
Emotional control	851 (72%)	0.678 (-0.796;2.152)	0.36	-0.861 (-2.500;0.778)	0.30
Working memory	845 (71%)	2.834 (1.196;4.471)	0.0007[c]	-2.016 (-3.761;-0.270)	0.023
Planning and organisation	847 (72%)	2.008 (0.426;3.590)	0.031	-1.139 (-2.807;0.529)	0.18
Meta-cognition index	842 (71%)	1.783 (0.145;3.421)	0.032	-1.957 (-3.694;-0.220)	0.027
Total score	841 (71%)	2.445 (0.882;4.008)	0.0022	-2.258 (-4.012;-0.504)	0.011
Emotional and behavioural problems as reported by parents/caregivers - T-score[e]					
Internalising problems	1014 (86%)	3.153 (1.705;4.600)	<0.0001[c]	-0.837 (-2.535;0.860)	0.33
Externalising problems	1014 (86%)	1.675 (0.261;3.088)	0.020	-1.715 (-3.325;-0.106)	0.036
Total problems	1014 (86%)	3.206 (1.757;4.655)	<0.0001[c]	-1.590 (-3.268;0.088)	0.063
Intelligence (range 45-155)[e]					
Total IQ	1066 (90%)	-5.508 (-7.254;-3.761)	<0.0001[c]	0.044 (-1.947;2.034)	0.96
Verbal IQ	1052 (89%)	-4.301 (-6.197;-2.405)	<0.0001[c]	0.237 (-1.980;2.455)	0.83
Performal IQ	1071 (90%)	-5.650 (-7.462;-3.838)	<0.0001[c]	-0.158 (-2.201;1.885)	0.87

Table 3 continued

Visual-motor integration (range 0.9-20)[f]	1097 (93%)	-0.925 (-1.256;-0.594)	<0.0001[c]	0.468 (0.087;0.850)	0.016
Alertness[e, g]					
Reaction time right hand - ms	413 (78%)	55.695 (6.319;105.071)	0.027	-55.418 (-121.649;10.813)	0.10
Within-person SD of repeated tests	413 (78%)	48.403 (0.632;96.174)	0.047	-34.167 (-91.313;22.978)	0.23
Reaction time left hand - ms	418 (79%)	54.996 (10.192;99.799)	0.016	-40.166 (-106.821;26.488)	0.23
Within-person SD of repeated tests	418 (79%)	49.624 (4.158;95.089)	0.032	-17.296 (-75.374;40.783)	0.55
Motor coordination (number of taps in 10 s)[f, g]					
Number of right hand taps	433 (82%)	-2.429 (-5.171;0.314)	0.081	0.863 (-2.181;3.907)	0.57
Number of left hand taps	433 (82%)	-1.536 (-4.077;1.004)	0.23	1.998 (-0.878;4.874)	0.17
Number of valid alternating taps	392 (74%)	0.707 (-4.391;5.805)	0.78	2.085 (-2.653;6.823)	0.38
Number of valid synchronous taps	418 (79%)	-1.354 (-3.998;1.289)	0.31	2.650 (-0.375;5.675)	0.085
Inhibition and flexibility[e, g]					
Difference in reaction time (inhibition) - ms	383 (72%)	25.177 (-51.033;101.387)	0.51	-53.416 (-125.105;18.274)	0.14
Difference in numbers of errors (inhibition)	385 (73%)	1.422 (-0.788;3.632)	0.20	-0.326 (-2.145;1.492)	0.72
Difference in reaction time (flexibility) - ms	369 (70%)	40.680 (-47.657;129.017)	0.36	-22.794 (-110.737;65.148)	0.60
Difference in numbers of errors (flexibility)	370 (70%)	2.085 (-0.062;4.231)	0.056	0.631 (-1.083;2.344)	0.46
Memory[f, g]					
Verbal-auditory					
Numbers (range 1-19)					
Memory span (forward)	331 (83%)	-1.113 (-1.883;-0.342)	0.0048	0.037 (-0.859;0.933)	0.93
Working memory (backward)	318 (80%)	-0.927 (-1.638;-0.216)	0.010	-0.393 (-1.286;0.500)	0.38
Word pairs (proportion of correct responses)					
Learning	287 (72%)	-0.065 (-0.121;-0.008)	0.025	0.039 (-0.027;0.104)	0.24
Immediate memory	285 (72%)	-0.110 (-0.165;-0.055)	0.0001[c]	0.047 (-0.014;0.109)	0.13
Delayed memory	282 (71%)	-0.078 (-0.132;-0.025)	0.0046	0.017 (-0.044;0.078)	0.57
Recognition	279 (70%)	-0.058 (-0.096;-0.021)	0.0027	0.035 (-0.013;0.083)	0.14
Non-verbal, visual-spatial					
Pictures (proportion of correct responses)	319 (80%)	-0.056 (-0.088;-0.024)	0.0006[c]	0.009 (-0.033;0.052)	0.66
Dots (proportion of correct responses)					
Learning	305 (77%)	-0.050 (-0.095;-0.005)	0.029	-0.016 (-0.064;0.032)	0.51
Immediate memory	305 (77%)	-0.051 (-0.114;0.012)	0.11	-0.013 (-0.077;0.052)	0.69

Table 3 continued

	Number (%) of available data per outcome before imputation (n=1191)	Beta-estimate or odds ratio (95% CI) for the comparison patients vs controls, adjusted for risk factors[a]	P-value	Beta-estimate or odds ratio (95% CI) for the comparison Late-PN vs Early-PN, adjusted for risk factors[b]	P-value
Delayed memory	299 (75%)	-0.058 (-0.122;0.006)	0.073	-0.002 (-0.069;0.064)	0.94
Learning index (range 50-150)	280 (71%)	-6.328 (-12.555;-0.101)	0.046	0.487 (-5.590;6.565)	0.87

Results are the combined beta-estimates and odds ratios from 31 datasets generated by multiple data imputation by chained equations under a missing-at-random assumption for the 786 post-PICU patients and 405 healthy control children. Sensitivity analyses to the missing-at-random assumption and with imputing worst test-scores for the severely disabled and thus non-testable children, as specified in the appendix, further supported the robustness of these results.

IQ = intelligence quotient; PeLOD score = Paediatric Logistic Organ Dysfunction Score; PICU = paediatric intensive care unit; PIM3 score = Paediatric Index of Mortality 3 score; PN = parenteral nutrition; SD = standard deviation; STRONGkids = Screening Tool Risk On Nutritional Status and Growth.

[a] Estimates and odds ratios were adjusted for the following risk factors: age, centre, race, sex, geographic origin, language, hand preference, history of malignancy, diabetes, a predefined syndrome, and the educational and occupational status of parents.

[b] Estimates and odds ratios were adjusted for the following risk factors: age, centre, race, sex, geographic origin, language, hand preference, history of malignancy, diabetes, a predefined syndrome, the educational and occupational status of parents, PIM3 score and PeLOD score upon PICU admission, STRONGkids risk category, and parental smoking behaviour prior to PICU admission.

[c] Statistically significant after Bonferroni correction for multiple comparisons.

[d] These values are odds ratios.

[e] Higher scores reflect worse performance.

[f] Higher scores reflect better performance.

[g] For alertness, motor coordination, executive functions, applicable imputation was limited to relevant age ranges.

Executive dysfunction comprises problems in complex decision making and goal-oriented behaviour with implications for daily life[183] and has been associated with externalising problems such as antisocial and aggressive behaviour.[171,184] Indeed, poor inhibitory control in children is known to contribute to impulsive and destructive behaviours that upset or harm others.[184] Hence, the possible beneficial effects of delaying PN in paediatric critical illness on the longer-term parent/caregiver-reported inhibitory function, further supported by better scores for other executive functions, externalising behaviour, and visual-motor integration (comparisons that lost significance after Bonferroni correction), are relevant. Indeed, the consequences for daily life and for the social environment are otherwise difficult to quantify by existing clinical neurocognitive tests.

The most robust protection of executive functioning of delayed PN was observed for the ability to suppress immediate responses, as measured by the parent/caregiver-reported inhibition score; this finding suggests potential damage induced by Early-PN to frontal lobe areas that coordinate inhibition.[185] The frontal lobe appears to be particularly vulnerable to metabolic insults during critical illness, with inflammation and neuronal damage described, which can be partially prevented by avoiding excessive hyperglycaemia.[186] A previous randomised, controlled trial[20] that documented the long-term neurocognitive impact of preventing hyperglycaemia in the PICU also found some improvement of executive functioning. We speculate that harm induced by Early-PN to executive functioning might also be a direct metabolic insult on the developing brains of young children, because it was not statistically explained by the acute effects of the intervention, such as increased incidence of new infections or delayed recovery, or by other potentially hazardous post-randomisation treatments given during the PICU stay, such as use of benzodiazepines. The larger benefit observed for critically ill infants than for older children provides support for this speculation. Whether other periods of age or development, such as puberty, also represent special vulnerability remains to be investigated.

Unlike our current findings in patients admitted to the PICU early in life, studies in other paediatric settings and otherwise healthy children have shown that insufficient rather than abundant nutritional intake, both prenatally and during childhood, can result in impaired growth and neurocognitive development.[84,187] These differing results could be explained by the context. Indeed, specifically in the context of critical illness, fasting-induced responses brought about during the first days after an insult might generate beneficial effects through (autophagy-induced) cell damage removal and prevention of neuronal loss.[132,186] The early administration of amino acids, the most powerful suppressors of autophagy,[132] rather than glucose or lipids was found to explain the short-term harm by Early-PN in critically ill children.[70] However, the exact underlying mechanisms of any long-term effect of not forcefully feeding patients early during critical illness remain speculative. Among others, alterations in DNA methylation in promoters or bodies of genes involved in neuronal growth, axonal guidance, and signal transduction could play a part,[188] since such epigenetic changes have been previously associated with executive dysfunction.[183] Moreover, the potential

involvement of telomere shortening, which has been shown to be accelerated by early initiation of PN during paediatric critical illness, should be further investigated.[126]

This study has limitations. First, the young age of PEPaNIC patients precluded complete and reliable results for certain neurocognitive tests. For these tests, the statistical power and thus the odds of identifying a difference between treatment groups was reduced. Second, neuroimaging studies were not done. Third, information on physiotherapy in the PICU and on the regular ward (i.e., after PICU but before hospital discharge) was not recorded. Fourth, data on follow-up consultations and therapies beyond the study protocol were not systematically available for all centres and all diagnostic subgroups. Fifth, after conservative Bonferroni correction, only the impact of withholding PN early in the PICU on long-term inhibitory control remained significant. However, given that inhibition is an important cognitive function involved in many aspects of daily life, and given the absence of any harm, this finding is relevant for endorsing implementation of withholding early PN in the PICU.

CONCLUSIONS

Patients admitted to the PICU early in life had worse outcomes at the 2-year follow-up for anthropometrics, health status, and neurocognitive development than did healthy control children. Withholding early PN for 1 week in the PICU did not negatively affect survival, anthropometrics, health status and neurocognitive development, and improved inhibitory control 2 years later.

APPENDIX

Methods S1: Definition of educational and occupational level of parents

Educational level of parents

The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): low (=1), middle (=2) and high (=3) educational level.

Occupational level of parents

The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (http://www.ilo.org/public/english/bureau/stat/isco/). In case one of the parents filled in two jobs in the questionnaire, the highest Isco code level was used. In case "unemployed", "disabled", "student", or "housewife/houseman" was filled in, an Isco code level of 1 was given to that parent. When the parents described their profession as "employee", "worker", "liberal profession", or "retired", they were given an Isco code level of 2.

Methods S2: Definition of "Syndrome"

A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development, and which is subdivided in the following categories:

- Genetically confirmed syndrome or pathogenic chromosomal abnormality
- Clearly defined syndrome, association or malformation without (identified) genetic aberration
- Polymalformative syndrome of unknown aetiology
- Clear auditory or visual impairment without specified syndrome
- Congenital hypothyroidism due to thyroid agenesis
- Brain tumour or tumour with intracranial metastatic disease
- Paedopsychiatric disorder (e.g. autism spectrum disorder, (treatment for) attention deficit hyperactivity disorder)
- Severe medical disorder, not primarily neurologic, but suspected to alter psychomotor and/or mental performance
- Severe neonatal problem (e.g. severe asphyxia)
- Severe craniocerebral trauma or near-drowning
- Severe infectious encephalitis or drug-induced encephalopathy
- Infectious meningitis, encephalitis or Guillain-Barré
- Resuscitation and/or need for extracorporeal membrane oxygenation prior to randomisation
- Severe convulsions or stroke prior to randomisation

Methods S3: Detailed description of outcome measures

Medical assessment

Anthropometric data

Height (in cm), body weight (in kg) and head circumference (in cm) were measured.

Health status

In an interview with the parents, the need for medical support of all kind during the past two years for healthy control children and during the 2 years following the index PICU admission for patients, was recorded. The hospital admissions because of surgery or a medical reason, and the occurrence of a psychiatric diagnosis were documented.

Clinical neurological examination

In order to assess whether there were gross neurological abnormalities, during a structured clinical neurological examination, signs of major neurologic dysfunction were detected in the following domains: interaction/language skills, gross motor function, involuntary movements, reflexes, coordination and balance, fine motor function, cranial nerves, and special senses (sensory, visual, and auditory function). These were all scored normal or abnormal. An abnormal result for each of these domains was given 1 point and the sum was made of all the abnormal results, with a range of 0-8.

Neurocognitive testing

A broad range of neurocognitive functions, including general intellectual functioning, visual-motor integration, attention, motor coordination, inhibitory control and cognitive flexibility, verbal and visual-spatial learning, and memory were evaluated, as previously reported.[20]

Patient/Parents-reported outcomes (PROs)

Executive functioning was measured with the Behaviour Rating Inventory of Executive Function (BRIEF-P 2.5-5 years, BRIEF 6-18 years), filled out by the parents or caregivers of the child. Overlapping scales and indices of both questionnaires (Inhibition, Flexibility, Emotional Control, Working Memory, Planning and Organisation, Meta-cognition) and a Total Score were analysed (T-scores, with mean 50 and SD 10).[171,172] Emotional and behavioural problems were assessed by the parent or caregiver with the Child Behaviour Checklist (CBCL 1.5-5 years or CBCL 6-18 years).[173,174] Internalising, externalising, and total problems were analysed (T-scores, with mean 50 and SD 10).[173,174]

Intelligence

General intellectual ability was assessed with use of age-appropriate versions of the Wechsler Intelligence Quotient (IQ) tests. The Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III-NL)[175] was used for children aged 2.5 years to 5 years 11 months (one version for age range 2 years 6 months to 3 years 11 months, and another version for age range 4 years

to 5 years 11 months), the Wechsler Intelligence Scale for Children (WISC-III-NL)[176] was used for children aged 6 years to 16 years 11 months, and the Wechsler Adult Intelligence Scale (WAIS-IV-NL)[177] for adolescents who were 17 years or older. For all these tests Total IQ, Verbal IQ, and Performal IQ scores (Test-mean 100, SD 15) were computed.

Visual-motor integration

We used the Beery Developmental Test of Visual-Motor Integration, 6th Edition (VMI) to assess the ability to integrate their visual and motor functions (total Scaled Score, Test-mean 10, SD 3). This involves eye-hand coordination.[178]

Alertness, motor-coordination, and executive functions

To measure alertness, motor-coordination and executive function, the validated Amsterdam Neuropsychological Tasks (ANT) program was used.[179] The ANT is a computer-aided assessment battery of reaction time (RT) tasks that allows for the systematic evaluation of information processing capacities.

Children 4 years and older performed ANT-Baseline Speed (BS), ANT-Tapping (TP), and Response Organisation Objects (ROO). The ANT-BS evaluated alertness by measuring simple RT to visual stimuli (mean RT and SD of RT were obtained for the right and left hand separately). The ANT-TP assessed motor coordination for the right hand, left hand, bimanual alternating, and bimanual synchronous. The ANT-ROO measured inhibitory control and cognitive flexibility by calculating the differences in RT and the differences in number of errors between tests of increasing demand.

Memory

Auditory/verbal memory and Visual-spatial/non-verbal memory were assessed with use of four tests from the Children's Memory Scale (CMS) for children between 5 and 16 years 11 months. [180] As to verbal memory, CMS-Numbers assessed short-term verbal memory span (forward digit recall) and verbal working memory load (backward digit recall). The CMS-Word Pairs (recall a list of word pairs) assessed short-term and long-term verbal memory, and recognition. As to non-verbal memory, CMS-Picture Locations (remembering and recall of pictures in various locations) assessed immediate visual memory. CMS-Dot Locations (remembering and recall of the location of dots) assessed immediate and delayed visual memory. For CMS-Numbers, raw scores for verbal memory span, CMS-numbers forward, and verbal working memory load, CMS-numbers backward were reported. For CMS-Word Pairs, CMS-Picture Locations, and CMS-Dot Locations, proportional scores were analysed (proportion of correct responses ranging from 0 to 1, with higher scores reflecting better performance). The CMS-Learning index is a standardised score of the sum of the three learning trials of the CMS-Word Pairs and the learning trial of the CMS-Dot Locations subtests. The range of the score is 50-150, with a higher score representing a better learning ability.

Methods S4: Imputation

Missing data (excluding the deceased and the severely disabled whereby non-testable children) were handled by ***multiple data imputation with chained equations under a 'missing at random' assumption***. There were no missing data in the baseline variables. Predictors for missing values included all covariates listed below, and were retained in the predictor models with a minimum correlation of 0.1 with the prediction target. Predictive mean matching[189] was used for numeric variables except for factors with two levels (which were imputed based on logistic regression) and factors with more than two levels (for which polytomous (unordered) regression was used). A monotonous visiting scheme was used such that variables for imputation were visited in increasing order of the number of missing data. Imputation convergence was assessed visually and set at 70 iterations (Figure S1). Since there were no more than 30% missing observations for all variables, 31 complete imputed datasets were used in the analyses,[181] and pooled results were obtained across datasets using Rubin's rules.[190]

Plausibility of the imputations was assessed visually via the densities of the observed data and that resulting from the imputed values (Figure S2). ***Sensitivity of results to the 'missing at random' assumption*** was assessed with use of pattern mixture models [190-192] assuming the original imputed values were either too high or too low by a factor of 0.1 for the main result of inhibition as reported by parents. Under this assumption, the obtained beta-estimates and P-values for randomisation to Late-PN vs. Early-PN for the multivariable linear regression analyses performed to determine significant and independent associations between risk factors and inhibition as reported by the parents at 2 years' follow-up within the tested patient population (Table S1-1) ranged from -2.962 ($p<0.0001$) to -2.396 ($p=0.032$). The effect-sizes thus remained of the same order of magnitude, sign, and statistical significance as were observed for the original imputed datasets, which suggested that the analyses were robust against the investigated 'missing at random' violation.

To further evaluate the robustness of the main findings**,** the analyses were repeated after imputing a ***penalised test result for all severely disabled and thus non-testable patients*****,** defined as the worst result in the observed patients or controls, plus or minus one, as appropriate for each test. In this case, the obtained beta-estimates (p-values) for randomisation to Late-PN vs. Early-PN for the multivariable linear regression analyses were respectively: A) -3.382 ($p<0.0001$) for inhibition as reported by parents; B) -1.928 ($p=0.031$) for meta-cognition as reported by parents; C) -1.992 ($P=0.026$) for working memory as reported by parents; D) -2.224 ($p=0.014$) for overall executive functioning as reported by parents; E) -1.668 ($p=0.045$) for externalising emotional and behavioural problems as reported by parents; and F) 0.464 ($p=0.017$) for visual-motor integration. These sensitivity analyses corresponded closely to the primary results as reported in Table 2 of the main manuscript.

All multiple data imputation analyses were performed with R version 3.4.3 and MICE version 2.46.0.

List of variables used for multiple data imputation by chained equations

Demographics of patients and control children and patient characteristics upon PICU admission

Centre, randomisation for Late-PN or Early-PN, patient vs. controls, race, gender, geographic origin, language, hand preference, history of malignancy, history of diabetes, a predefined "syndrome", educational and occupational status of parents, diagnosis, PIM3 and PeLOD scores upon PICU admission, risk of malnutrition (STRONGkids category), parental smoking behaviour prior to PICU admission, age at randomisation, age group at randomisation.

Acute effects of randomisation and post-randomisation treatments in PICU

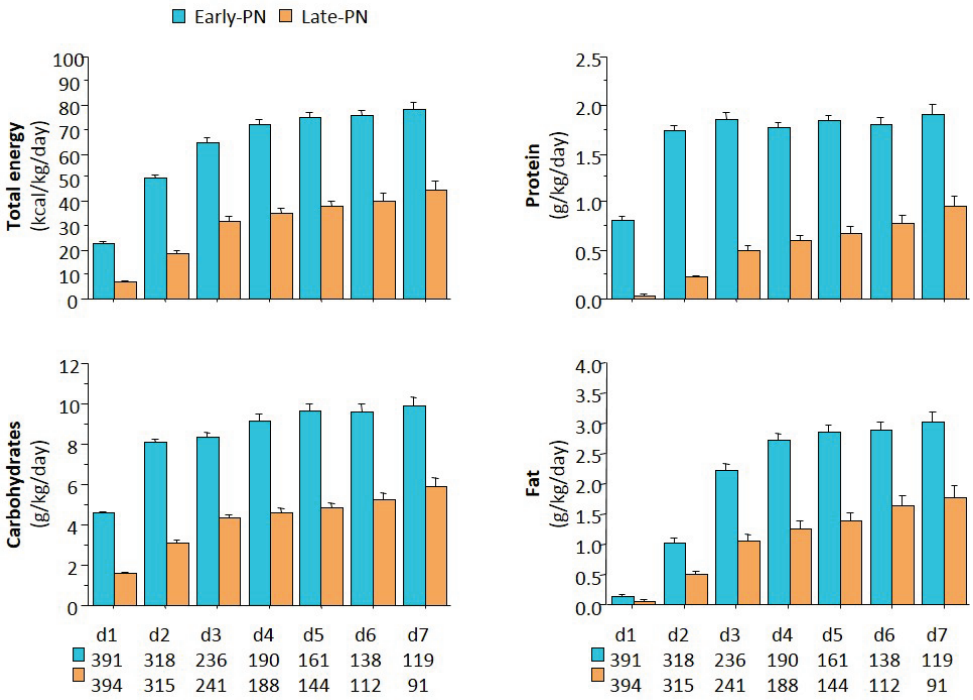
Acquisition of new PICU infections, duration of PICU stay, duration of mechanical ventilatory support, hypoglycaemia, duration of treatment with haemodynamic support, antibiotics, corticosteroids, opioids, benzodiazepines, hypnotics and α2-agonists.

At 2-years' follow-up

Age, test location, height, weight, head circumference, composite endpoint "diagnosed with a somatic illness", composite endpoint "diagnosed with a psychiatric illness", composite endpoint "admitted to hospital for a medical or surgical reason", clinical neurological examination, verbal IQ, performal IQ, total IQ, visual motor integration, reaction time left hand, reaction time right hand, within subject SD of reaction time left hand, within subject SD of reaction time left hand, number of unimanual taps right hand, number of unimanual taps left hand, number of valid alternating taps, number of valid synchronous taps, delta reaction time inhibition, delta number of errors inhibition, delta reaction time flexibility, delta number of errors flexibility, numbers memory span forward, numbers working memory backward, word pairs learning, word pairs immediate memory, word pairs delayed memory, word pairs recognition, pictures, dots learning, dots immediate memory, dots delayed memory, learning index, executive functioning as reported by parents/caregivers (inhibition, flexibility, emotional control, working memory, planning and organisation, meta-cognition index, and total score), emotional and behavioural problems as reported by parents/caregivers (internalising problems, externalising problems, and total problems).

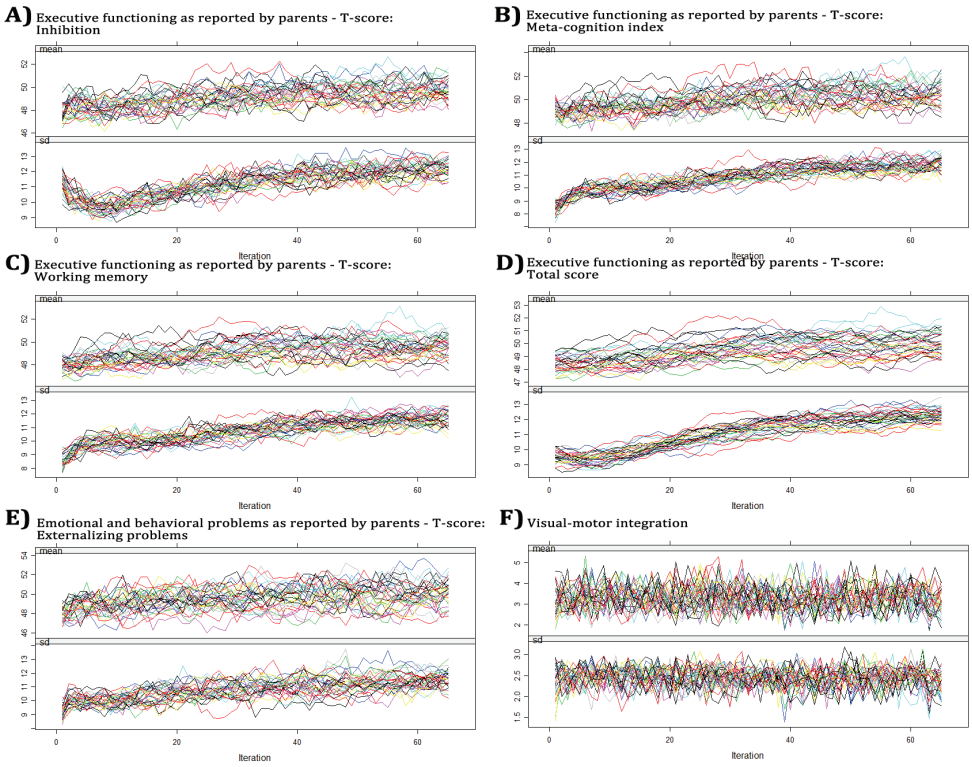
Interactions between age group and randomization were not included in the imputation models.

Figure S1: Macronutrient doses during the first week in PICU administered to the tested population



Daily amount of total energy in kcal/kg/day, and the daily amounts of total substrates in g/kg/day are shown for the first 7 days in the paediatric intensive care unit (PICU). Bars represent the mean and the whiskers represent the standard error of the mean (SEM). The red bars represent the Early-PN group and the green bars represent the Late-PN group.

Figure S2: Imputation convergence for selected neurocognitive test results



Mean and standard deviation of imputed values in each of 31 datasets over 70 iterations for

A) Executive functioning as reported by parents/caregivers - T-score: Inhibition;

B) Meta-cognition index;

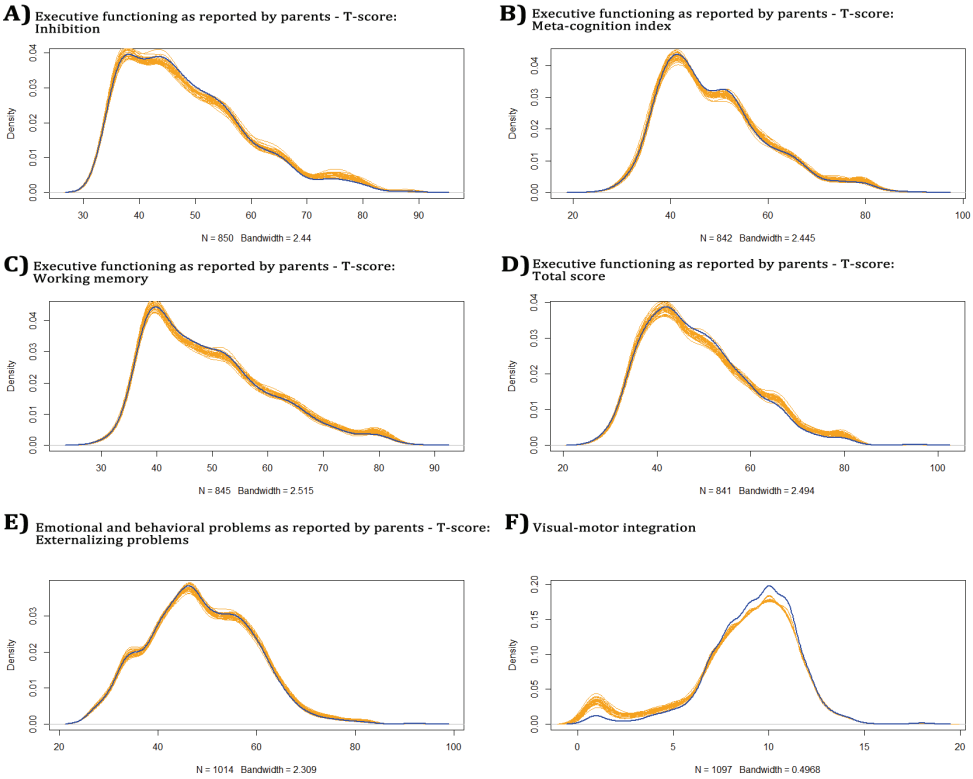
C) Working memory;

D) Total score;

E) Emotional and behavioural problems as reported by parents/caregivers - T-score: Externalising problems;

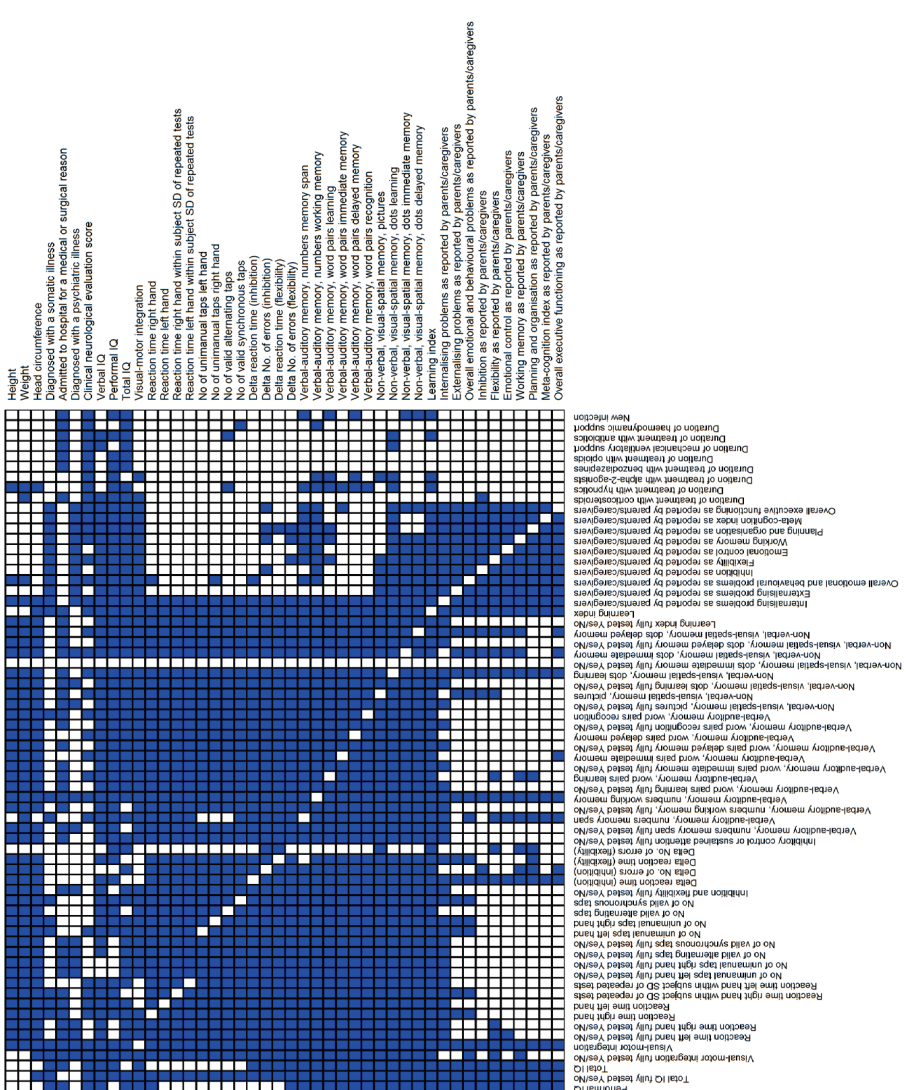
F) Visual-motor integration.

Figure S3: Density estimates of the observed and imputed values for selected neurocognitive test results



Density estimated for observed values (in blue) and for each imputed dataset (in orange) for
A) Executive functioning as reported by parents/caregivers - T-score: Inhibition;
B) Meta-cognition index;
C) Working memory;
D) Total score;
E) Emotional and behavioural problems as reported by parents - T-score: Externalising problems;
F) Visual-motor integration.

Figure S4: Multiple imputation predictor variables



Missing values for the variables in each row are imputed based on models that use as predictors only the column variables highlighted in blue. The predictor variables are selected as described in Methods S4.

Table S1: Multivariable linear regression analyses determining significant and independent associations between risk factors and long-term test results within the tested patient population

Table S1-1: Multivariable linear regression analyses determining significant and independent associations between risk factors and inhibition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	Beta-estimate	Confidence interval		P-value	Beta-estimate	Confidence interval		P-value
Randomisation to late vs. early initiation of PN	***-3.422***	***-5.171***	***-1.673***	***0.00013***	***-3.373***	***-5.140***	***-1.605***	***0.00020***
Centre								
Leuven vs. Edmonton	1.752	-5.864	9.369	0.65	2.306	-5.392	10.004	0.55
Rotterdam vs. Edmonton	1.683	-6.012	9.377	0.66	1.307	-6.456	9.069	0.74
Male vs. female sex	1.098	-0.740	2.937	0.24	1.162	-0.675	2.999	0.21
Right vs. left hand preference	0.280	-2.548	3.109	0.84	0.284	-2.492	3.060	0.83
Medium vs. high STRONGkids risk level[a]	0.592	-2.543	3.726	0.71	0.562	-2.620	3.745	0.72
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-0.800	-4.510	2.911	0.67	-0.634	-4.338	3.070	0.73
Burns	-1.969	-17.860	13.923	0.80	-3.540	-19.912	12.833	0.67
Neurosurgery - traumatic brain injury	1.988	-1.662	5.638	0.28	1.640	-2.005	5.285	0.37
Thoracic	-1.293	-5.670	3.084	0.56	-1.225	-5.650	3.200	0.58
Transplantation	5.434	-2.598	13.465	0.18	3.995	-5.157	13.148	0.38
Orthopaedic surgery-trauma	0.485	-5.186	6.157	0.86	0.184	-5.522	5.889	0.94
Other	3.419	-1.470	8.309	0.17	2.611	-2.369	7.591	0.30
Medical								
Cardiac	2.694	-2.638	8.026	0.32	2.291	-3.295	7.877	0.42
Gastrointestinal-hepatic	10.927	-5.325	27.179	0.18	10.591	-5.610	26.792	0.19
Haematologic-oncologic	3.951	-4.925	12.828	0.38	0.637	-8.789	10.063	0.89
Neurologic	0.691	-3.535	4.918	0.74	-0.297	-4.658	4.064	0.89
Respiratory	0.374	-3.370	4.118	0.84	-0.161	-4.032	3.710	0.93
Other	0.096	-4.640	4.832	0.96	-0.307	-5.197	4.582	0.90

Table S1-1 continued

Infant (age<1y) vs. child at randomisation	0.315	-1.635	2.265	0.75	0.331	-1.719	2.382	0.75
Malignancy vs. no malignancy	-1.620	-5.794	2.554	0.44	-1.907	-6.129	2.314	0.37
Diabetes vs. no diabetes	-5.169	-28.229	17.890	0.65	-3.412	-26.465	19.642	0.77
Syndrome vs. no syndrome[b]	3.447	0.314	6.581	0.031	3.727	0.571	6.884	0.020
PIM3 score (per point added)[c]	0.071	-0.780	0.922	0.87	-0.006	-0.883	0.871	0.98
PeLOD score first 24 hrs (per point added)[d]	0.067	-0.047	0.181	0.24	0.051	-0.064	0.167	0.38
Known non-European origin vs. other[e]	-0.582	-4.367	3.202	0.76	-0.625	-4.407	3.158	0.74
Known non-Caucasian vs. other[e]	-1.931	-6.585	2.724	0.41	-1.560	-6.231	3.112	0.51
Known not exclusive Dutch or English language vs. other	0.359	-2.480	3.198	0.80	0.379	-2.456	3.214	0.79
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.090	-8.471	2.292	0.25	-2.468	-7.907	2.970	0.37
Educational level 2	-2.097	-6.648	2.453	0.36	-1.634	-6.226	2.958	0.48
Educational level 2.5	-3.730	-8.625	1.164	0.13	-3.127	-8.047	1.792	0.21
Educational level 3	-4.590	-9.509	0.329	0.067	-4.043	-8.996	0.909	0.10
Educational level unknown	-0.579	-6.400	5.242	0.84	-0.111	-5.963	5.742	0.97
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	3.634	-4.260	11.527	0.36	3.091	-4.810	10.992	0.44
Occupational level 2	3.086	-4.721	10.893	0.43	2.380	-5.448	10.208	0.55
Occupational level 2.5	3.803	-4.335	11.941	0.35	2.995	-5.176	11.166	0.47
Occupational level 3	3.047	-4.923	11.017	0.45	2.400	-5.583	10.382	0.55
Occupational level 3.5	0.490	-7.969	8.950	0.90	-0.224	-8.701	8.253	0.95
Occupational level 4	4.074	-4.163	12.312	0.33	3.139	-5.147	11.426	0.45
Occupational level unknown	2.458	-5.483	10.399	0.54	1.882	-6.074	9.839	0.64
Parental smoking between birth and PICU admission vs. no smoking	1.530	-0.787	3.847	0.19	1.635	-0.671	3.942	0.16
New infection vs. no new infection					-0.420	-3.898	3.058	0.81
Duration of stay in the PICU (per day added)					0.033	-0.258	0.323	0.82
Days with hypoglycaemic event (per day added)					-0.331	-2.299	1.637	0.74

Table S1-1 continued

	Model adjusted for risk factors			Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	**Beta-estimate**	**Confidence interval**	**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Duration of mechanical ventilatory support (per day added)				-0.089	-0.291	0.113	0.38
Duration of treatment with antibiotics (per day added)				-0.049	-0.321	0.223	0.72
Duration of haemodynamic support (per day added)				-0.100	-0.305	0.104	0.33
Duration of treatment with corticosteroids (per day added)				0.229	-0.101	0.558	0.17
Duration of treatment with opioids (per day added)				-0.082	-0.368	0.204	0.57
Duration of treatment with benzodiazepines (per day added)				0.323	0.056	0.590	0.017
Duration of treatment with hypnotics (per day added)				0.073	-0.211	0.356	0.61
Duration of treatment with α2-agonists (per day added)				-0.186	-0.449	0.078	0.16

PeLOD = paediatric logistic organ dysfunction score; PICU = paediatric intensive care unit; PIM3 = paediatric index of mortality 3 score; PN = parenteral nutrition.

For inhibition as reported by parents, higher scores reflect worse performance.

[a]Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[b]A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2)

[c]Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.

[d]Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.

[e]Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[182]

[f]The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).

[g]The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-2: Multivariable linear regression analyses determining significant and independent associations between risk factors and working memory as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	Beta-estimate	Confidence interval		P-value	Beta-estimate	Confidence interval		P-value
Randomisation to late vs. early initiation of PN	***-2.016***	***-3.761***	***-0.270***	***0.023***	***-1.961***	***-3.728***	***-0.194***	***0.029***
Centre								
Leuven vs. Edmonton	0.686	-6.879	8.250	0.85	1.356	-6.400	9.112	0.73
Rotterdam vs. Edmonton	0.107	-7.564	7.779	0.97	-0.082	-7.943	7.778	0.98
Male vs. female sex	1.266	-0.523	3.055	0.16	1.220	-0.564	3.005	0.17
Right vs. left hand preference	0.222	-2.353	2.797	0.86	0.287	-2.274	2.849	0.82
Medium vs. high STRONGkids risk level [a]	-0.120	-3.331	3.092	0.94	0.180	-3.084	3.444	0.91
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-2.737	-6.574	1.100	0.16	-2.573	-6.423	1.277	0.18
Burns	-1.793	-17.437	13.850	0.82	-2.819	-18.998	13.361	0.73
Neurosurgery - traumatic brain injury	2.159	-1.515	5.833	0.24	1.930	-1.752	5.612	0.30
Thoracic	-3.357	-7.670	0.956	0.12	-3.286	-7.666	1.094	0.14
Transplantation	6.273	-1.387	13.934	0.10	5.872	-2.856	14.599	0.18
Orthopaedic surgery-trauma	0.651	-4.851	6.153	0.81	0.536	-4.962	6.034	0.84
Other	4.021	-0.885	8.927	0.10	3.462	-1.543	8.467	0.17
Medical								
Cardiac	3.986	-1.280	9.252	0.13	3.125	-2.477	8.727	0.27
Gastrointestinal-hepatic	13.673	-1.652	28.999	0.080	13.484	-1.816	28.784	0.083
Haematologic-oncologic	-1.926	-10.690	6.838	0.66	-4.287	-13.541	4.967	0.36
Neurologic	0.246	-3.909	4.402	0.90	-0.369	-4.582	3.843	0.86
Respiratory	-2.172	-5.908	1.563	0.25	-2.735	-6.583	1.113	0.16
Other	-1.210	-5.913	3.493	0.61	-1.545	-6.405	3.314	0.53

Table S1-2 continued

	Model adjusted for risk factors				Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Infant (age<1y) vs. child at randomisation	-0.737	-2.690	1.216	0.45	-0.703	-2.721	1.315	0.49
Malignancy vs. no malignancy	1.704	-2.413	5.821	0.41	1.688	-2.471	5.847	0.42
Diabetes vs. no diabetes	0.527	-22.272	23.326	0.96	1.951	-20.856	24.757	0.86
Syndrome vs. no syndrome[b]	5.298	2.181	8.414	0.00094	5.324	2.167	8.481	0.0010
PIM3 score (per point added)[c]	0.280	-0.614	1.173	0.53	0.191	-0.737	1.120	0.68
PeLOD score first 24 hrs (per point added)[d]	0.011	-0.101	0.124	0.84	-0.004	-0.118	0.110	0.94
Known non-European origin vs. other[e]	1.118	-2.771	5.007	0.57	1.112	-2.781	5.005	0.57
Known non-Caucasian vs. other[e]	-3.969	-9.097	1.158	0.12	-3.744	-8.870	1.382	0.15
Known not exclusive Dutch or English language vs. other	0.316	-2.338	2.970	0.81	0.365	-2.305	3.036	0.78
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.391	-8.554	1.773	0.19	-2.870	-8.119	2.379	0.28
Educational level 2	-2.230	-6.603	2.144	0.31	-1.745	-6.159	2.669	0.43
Educational level 2.5	-3.950	-8.584	0.683	0.094	-3.314	-7.974	1.346	0.16
Educational level 3	-4.174	-8.873	0.524	0.081	-3.631	-8.376	1.114	0.13
Educational level unknown	-1.527	-7.153	4.099	0.59	-1.042	-6.754	4.669	0.71
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	0.618	-7.159	8.394	0.87	0.162	-7.632	7.956	0.96
Occupational level 2	0.579	-7.203	8.362	0.88	0.055	-7.752	7.863	0.98
Occupational level 2.5	0.286	-7.808	8.381	0.94	-0.453	-8.571	7.665	0.91
Occupational level 3	-0.860	-8.803	7.082	0.83	-1.442	-9.390	6.506	0.72
Occupational level 3.5	-3.143	-11.577	5.292	0.46	-3.740	-12.188	4.708	0.38
Occupational level 4	0.358	-7.869	8.585	0.93	-0.426	-8.692	7.840	0.91
Occupational level unknown	0.378	-7.667	8.422	0.92	-0.162	-8.241	7.918	0.96

Table S1-2 continued

Parental smoking between birth and PICU admission vs. no smoking	1.230	-1.255	3.715	0.32	1.315	-1.174	3.803	0.29
New infection vs. no new infection					0.674	-2.783	4.131	0.70
Duration of stay in the PICU (per day added)					0.001	-0.287	0.289	0.99
Days with hypoglycaemic event (per day added)					-0.166	-2.167	1.835	0.87
Duration of mechanical ventilatory support (per day added)					-0.103	-0.300	0.095	0.30
Duration of treatment with antibiotics (per day added)					0.034	-0.239	0.307	0.80
Duration of haemodynamic support (per day added)					-0.066	-0.266	0.134	0.51
Duration of treatment with corticosteroids (per day added)					0.095	-0.226	0.415	0.56
Duration of treatment with opioids (per day added)					-0.150	-0.435	0.134	0.29
Duration of treatment with benzodiazepines (per day added)					0.337	0.075	0.598	0.011
Duration of treatment with hypnotics (per day added)					0.066	-0.214	0.346	0.64
Duration of treatment with $\alpha 2$-agonists (per day added)					-0.207	-0.465	0.050	0.11

PeLOD = Paediatric Logistic Organ Dysfunction score; PICU = paediatric intensive care unit; PIM3 = Paediatric Index of Mortality 3 score; PN = parenteral nutrition.
For working memory as reported by parents, higher scores reflect worse performance.

[a]Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[b]A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2)

[c]Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.

[d]Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.

[e]Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[182]

[f]The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).

[g]The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-3: Multivariable linear regression analyses determining significant and independent associations between risk factors and meta-cognition as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	Beta-estimate	Confidence interval		P-value	Beta-estimate	Confidence interval		P-value
Randomisation to late vs. early initiation of PN	***-1.957***	***-3.694***	***-0.220***	***0.027***	***-1.914***	***-3.668***	***-0.159***	***0.032***
Centre								
Leuven vs. Edmonton	1.562	-5.918	9.041	0.68	2.358	-5.310	10.026	0.54
Rotterdam vs. Edmonton	0.874	-6.632	8.380	0.81	0.959	-6.726	8.644	0.80
Male vs. female sex	0.936	-0.884	2.755	0.31	0.883	-0.934	2.699	0.33
Right vs. left hand preference	0.355	-2.296	3.006	0.79	0.456	-2.136	3.049	0.72
Medium vs. high STRONGkids risk level[a]	-0.073	-3.217	3.071	0.96	0.190	-3.019	3.398	0.90
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-2.385	-6.209	1.438	0.22	-2.290	-6.145	1.565	0.24
Burns	-0.358	-16.758	16.043	0.96	-1.153	-18.197	15.892	0.89
Neurosurgery - traumatic brain injury	1.129	-2.417	4.674	0.53	0.907	-2.639	4.453	0.61
Thoracic	-3.311	-7.540	0.919	0.12	-3.228	-7.490	1.034	0.13
Transplantation	5.501	-2.154	13.157	0.15	5.628	-3.204	14.460	0.20
Orthopaedic surgery-trauma	1.015	-4.352	6.381	0.71	0.939	-4.431	6.310	0.73
Other	3.183	-1.648	8.015	0.19	2.623	-2.336	7.581	0.29
Medical								
Cardiac	2.776	-2.502	8.053	0.30	2.040	-3.474	7.553	0.46
Gastrointestinal-hepatic	13.837	-1.403	29.076	0.074	13.620	-1.592	28.832	0.079
Haematologic-oncologic	0.069	-8.634	8.773	0.98	-1.756	-11.000	7.488	0.70
Neurologic	-0.205	-4.378	3.967	0.92	-0.703	-4.941	3.536	0.74
Respiratory	-1.146	-5.067	2.776	0.56	-1.620	-5.670	2.430	0.43
Other	-1.400	-6.082	3.282	0.55	-1.681	-6.540	3.179	0.49

Table S1-3 continued

Infant (age<1y) vs. child at randomisation	-0.047	-1.996	1.901	0.96	-0.008	-2.034	2.017	0.99
Malignancy vs. no malignancy	0.192	-3.858	4.243	0.92	0.267	-3.816	4.350	0.89
Diabetes vs. no diabetes	2.021	-20.625	24.666	0.86	3.172	-19.481	25.826	0.78
Syndrome vs. no syndrome[b]	4.615	1.484	7.746	0.0040	4.650	1.463	7.838	0.0044
PIM3 score (per point added)[c]	0.140	-0.764	1.044	0.76	0.057	-0.887	1.002	0.90
PeLOD score first 24 hrs (per point added)[d]	0.005	-0.111	0.121	0.93	-0.011	-0.128	0.106	0.85
Known non-European origin vs. other [e]	1.902	-2.060	5.864	0.34	1.933	-2.039	5.904	0.33
Known non-Caucasian vs. other[e]	-4.294	-9.338	0.750	0.094	-4.159	-9.193	0.874	0.10
Known not exclusive Dutch or English language vs. other	-0.479	-3.185	2.227	0.72	-0.525	-3.243	2.193	0.70
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.383	-8.510	1.743	0.19	-2.849	-8.040	2.342	0.28
Educational level 2	-2.252	-6.601	2.098	0.30	-1.850	-6.234	2.533	0.40
Educational level 2.5	-3.961	-8.586	0.663	0.092	-3.364	-8.009	1.280	0.15
Educational level 3	-3.754	-8.451	0.943	0.11	-3.251	-7.998	1.496	0.17
Educational level unknown	-2.156	-7.533	3.221	0.42	-1.668	-7.105	3.770	0.54
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	1.617	-6.176	9.410	0.68	1.218	-6.597	9.034	0.75
Occupational level 2	1.903	-5.876	9.682	0.63	1.382	-6.410	9.174	0.72
Occupational level 2.5	1.416	-6.695	9.528	0.73	0.718	-7.412	8.847	0.86
Occupational level 3	0.828	-7.068	8.724	0.83	0.237	-7.661	8.135	0.95
Occupational level 3.5	-2.904	-11.297	5.489	0.49	-3.499	-11.894	4.896	0.41
Occupational level 4	1.026	-7.130	9.183	0.80	0.218	-7.962	8.399	0.95
Occupational level unknown	1.409	-6.541	9.359	0.72	0.899	-7.064	8.861	0.82
Parental smoking between birth and PICU admission vs. no smoking	0.770	-1.592	3.131	0.51	0.858	-1.503	3.219	0.47
New infection vs. no new infection					0.261	-3.320	3.843	0.88
Duration of stay in the PICU (per day added)					-0.042	-0.328	0.244	0.77
Days with hypoglycaemic event (per day added)					-0.262	-2.237	1.714	0.79

Table S1-3 continued

	Model adjusted for risk factors			Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	**Beta-estimate**	**Confidence interval**	**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Duration of mechanical ventilatory support (per day added)				-0.090	-0.288	0.108	0.36
Duration of treatment with antibiotics (per day added)				0.070	-0.206	0.346	0.61
Duration of haemodynamic support (per day added)				-0.048	-0.249	0.153	0.63
Duration of treatment with corticosteroids (per day added)				0.053	-0.279	0.386	0.75
Duration of treatment with opioids (per day added)				-0.103	-0.389	0.183	0.48
Duration of treatment with benzodiazepines (per day added)				0.328	0.067	0.590	0.014
Duration of treatment with hypnotics (per day added)				0.032	-0.254	0.319	0.82
Duration of treatment with α2-agonists (per day added)				-0.235	-0.495	0.025	0.076

PeLOD = Paediatric Logistic Organ Dysfunction score; PICU = paediatric intensive care unit; PIM3 = Paediatric Index of Mortality 3 score; PN = parenteral nutrition.

For meta-cognition as reported by parents, higher scores reflect worse performance.

[a] Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[b] A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2).

[c] Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.

[d] Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.

[e] Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[182]

[f] The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).

[g] The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-4: Multivariable linear regression analyses determining significant and independent associations between risk factors and overall executive functioning as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	Beta-estimate	Confidence interval		P-value	Beta-estimate	Confidence interval		P-value
Randomisation to late vs. early initiation of PN	***-2.258***	***-4.012***	***-0.504***	***0.011***	***-2.181***	***-3.953***	***-0.409***	***0.015***
Centre								
Leuven vs. Edmonton	3.856	-3.580	11.291	0.30	4.479	-3.043	12.001	0.24
Rotterdam vs. Edmonton	3.164	-4.370	10.699	0.40	2.874	-4.744	10.493	0.45
Male vs. female sex	0.990	-0.826	2.806	0.28	0.977	-0.841	2.796	0.29
Right vs. left hand preference	0.295	-2.397	2.986	0.82	0.404	-2.232	3.039	0.76
Medium vs. high STRONGkids risk level[a]	-0.324	-3.425	2.777	0.83	-0.053	-3.211	3.106	0.97
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	-2.051	-5.824	1.722	0.28	-1.943	-5.732	1.847	0.31
Burns	1.883	-14.275	18.041	0.81	0.303	-16.376	16.983	0.97
Neurosurgery - traumatic brain injury	2.165	-1.441	5.770	0.23	1.896	-1.712	5.505	0.30
Thoracic	-1.916	-6.216	2.383	0.38	-1.812	-6.154	2.529	0.41
Transplantation	6.550	-0.796	13.896	0.080	6.490	-1.812	14.793	0.12
Orthopaedic surgery-trauma	0.235	-5.239	5.710	0.93	0.026	-5.466	5.517	0.99
Other	4.937	0.015	9.858	0.049	4.123	-0.923	9.168	0.10
Medical								
Cardiac	2.858	-2.373	8.089	0.28	1.891	-3.581	7.362	0.49
Gastrointestinal-hepatic	13.977	-1.084	29.038	0.068	13.632	-1.377	28.640	0.074
Haematologic-oncologic	1.544	-7.245	10.333	0.73	-0.418	-9.711	8.875	0.92
Neurologic	-0.445	-4.596	3.706	0.83	-1.077	-5.314	3.160	0.61
Respiratory	-0.999	-4.628	2.631	0.58	-1.492	-5.206	2.223	0.42
Other	-0.949	-5.599	3.701	0.68	-1.363	-6.189	3.464	0.57

Table S1-4 continued

	Model adjusted for risk factors				Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Infant (age<1y) vs. child at randomisation	0.317	-1.608	2.242	0.74	0.386	-1.634	2.406	0.70
Malignancy vs. no malignancy	-0.038	-4.162	4.085	0.98	-0.131	-4.290	4.028	0.95
Diabetes vs. no diabetes	2.475	-20.377	25.328	0.83	4.192	-18.640	27.025	0.71
Syndrome vs. no syndrome[b]	5.082	2.013	8.152	0.0012	5.296	2.202	8.390	0.00086
PIM3 score (per point added)[c]	0.194	-0.695	1.082	0.66	0.121	-0.805	1.048	0.79
PeLOD score first 24 hrs (per point added)[d]	0.026	-0.089	0.140	0.66	0.009	-0.107	0.125	0.88
Known non-European origin vs. other[e]	1.782	-2.000	5.563	0.35	1.779	-2.001	5.559	0.35
Known non-Caucasian vs. other[e]	-4.530	-9.283	0.222	0.061	-4.265	-9.022	0.492	0.078
Known not exclusive Dutch or English language vs. other	0.066	-2.585	2.718	0.96	-0.003	-2.665	2.659	0.99
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	-3.958	-9.112	1.196	0.13	-3.283	-8.492	1.927	0.21
Educational level 2	-2.614	-7.009	1.782	0.24	-2.119	-6.552	2.314	0.34
Educational level 2.5	-4.118	-8.777	0.541	0.083	-3.422	-8.103	1.259	0.15
Educational level 3	-4.625	-9.360	0.111	0.055	-4.032	-8.806	0.742	0.097
Educational level unknown	-0.202	-5.678	5.273	0.94	0.386	-5.139	5.910	0.89
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	2.929	-4.880	10.738	0.46	2.240	-5.573	10.053	0.57
Occupational level 2	3.469	-4.305	11.244	0.38	2.652	-5.129	10.433	0.50
Occupational level 2.5	3.334	-4.693	11.361	0.41	2.298	-5.752	10.348	0.57
Occupational level 3	2.959	-4.955	10.873	0.46	2.159	-5.758	10.077	0.59
Occupational level 3.5	-0.484	-8.917	7.948	0.91	-1.317	-9.760	7.125	0.75
Occupational level 4	3.326	-4.857	11.508	0.42	2.245	-5.979	10.468	0.59
Occupational level unknown	2.792	-5.114	10.698	0.48	2.085	-5.836	10.006	0.60

Table S1-4 continued

Parental smoking between birth and PICU admission vs. no smoking	1.022	-1.242	3.285	0.37	1.144	-1.108	3.396	0.31
New infection vs. no new infection					-0.356	-3.782	3.070	0.83
Duration of stay in the PICU (per day added)					0.045	-0.236	0.326	0.75
Days with hypoglycaemic event (per day added)					-0.670	-2.632	1.293	0.50
Duration of mechanical ventilatory support (per day added)					-0.123	-0.323	0.076	0.22
Duration of treatment with antibiotics (per day added)					-0.017	-0.282	0.247	0.89
Duration of haemodynamic support (per day added)					-0.071	-0.272	0.130	0.48
Duration of treatment with corticosteroids (per day added)					0.073	-0.251	0.396	0.65
Duration of treatment with opioids (per day added)					-0.102	-0.381	0.177	0.47
Duration of treatment with benzodiazepines (per day added)					0.368	0.111	0.625	0.0050
Duration of treatment with hypnotics (per day added)					0.078	-0.206	0.363	0.58
Duration of treatment with $\alpha 2$-agonists (per day added)					-0.260	-0.516	-0.003	0.047

PeLOD = Paediatric Logistic Organ Dysfunction score; PICU = paediatric intensive care unit; PIM3 = Paediatric Index of Mortality 3 score; PN = parenteral nutrition.
For overall executive functioning as reported by parents, higher scores reflect worse performance.

[a]Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[b]A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2).

[c]Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.

[d]Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.

[e]Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[182]

[f]The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).

[g]The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-5: Multivariable linear regression analyses determining significant and independent associations between risk factors and externalising problems as reported by the parents/caregivers at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	Beta-estimate	Confidence interval		P-value	Beta-estimate	Confidence interval		P-value
Randomisation to late vs. early initiation of PN	***-1.715***	***-3.325***	***-0.106***	***0.036***	***-1.810***	***-3.441***	***-0.179***	***0.029***
Centre								
Leuven vs. Edmonton	4.664	-1.959	11.287	0.16	4.377	-2.421	11.175	0.20
Rotterdam vs. Edmonton	3.024	-3.740	9.787	0.37	2.464	-4.455	9.383	0.48
Male vs. female sex	1.483	-0.241	3.207	0.091	1.427	-0.303	3.157	0.10
Right vs. left hand preference	0.103	-2.410	2.616	0.93	0.159	-2.327	2.645	0.89
Medium vs. high STRONGkids risk level[a]	-0.069	-2.880	2.742	0.96	0.170	-2.702	3.042	0.90
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	0.597	-2.874	4.068	0.73	0.672	-2.793	4.138	0.70
Burns	8.641	-6.396	23.679	0.25	8.965	-6.524	24.454	0.25
Neurosurgery - traumatic brain injury	3.809	0.528	7.089	0.022	3.699	0.412	6.985	0.027
Thoracic	-1.001	-5.006	3.004	0.62	-0.765	-4.811	3.280	0.70
Transplantation	7.503	0.677	14.328	0.031	8.683	0.985	16.381	0.027
Orthopaedic surgery-trauma	-0.017	-5.137	5.102	0.99	-0.105	-5.263	5.053	0.96
Other	2.924	-1.639	7.487	0.20	2.192	-2.432	6.815	0.35
Medical								
Cardiac	2.955	-2.044	7.954	0.24	2.199	-3.080	7.479	0.41
Gastrointestinal-hepatic	10.723	-4.646	26.091	0.17	10.571	-4.771	25.913	0.17
Haematologic-oncologic	7.972	-0.416	16.361	0.062	7.727	-1.147	16.600	0.087
Neurologic	2.384	-1.535	6.303	0.23	2.119	-1.908	6.146	0.30
Respiratory	1.392	-1.909	4.693	0.40	1.040	-2.386	4.467	0.55
Other	-0.018	-4.367	4.330	0.99	-0.257	-4.787	4.273	0.91

Table S1-5 continued

	Model adjusted for risk factors			Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	Beta-estimate	Confidence interval	P-value	Beta-estimate	Confidence interval		P-value
Duration of mechanical ventilatory support (per day added)				-0.113	-0.295	0.070	0.22
Duration of treatment with antibiotics (per day added)				-0.062	-0.314	0.189	0.62
Duration of haemodynamic support (per day added)				-0.101	-0.286	0.084	0.28
Duration of treatment with corticosteroids (per day added)				-0.055	-0.363	0.253	0.72
Duration of treatment with opioids (per day added)				-0.111	-0.371	0.150	0.40
Duration of treatment with benzodiazepines (per day added)				0.304	0.064	0.544	0.013
Duration of treatment with hypnotics (per day added)				0.042	-0.226	0.310	0.76
Duration of treatment with α2-agonists (per day added)				-0.200	-0.446	0.046	0.11

PeLOD = Paediatric Logistic Organ Dysfunction score; PICU = paediatric intensive care unit; PIM3 = Paediatric Index of Mortality 3 score; PN = parenteral nutrition.
For externalising problems as reported by parents, higher scores reflect worse performance.

[a] Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[b] A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2).

[c] Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.

[d] Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.

[e] Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[182]

[f] The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).

[g] The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-5 continued

	Model adjusted for risk factors			Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	Beta-estimate	Confidence interval	P-value	Beta-estimate	Confidence interval		P-value
Duration of mechanical ventilatory support (per day added)				-0.113	-0.295	0.070	0.22
Duration of treatment with antibiotics (per day added)				-0.062	-0.314	0.189	0.62
Duration of haemodynamic support (per day added)				-0.101	-0.286	0.084	0.28
Duration of treatment with corticosteroids (per day added)				-0.055	-0.363	0.253	0.72
Duration of treatment with opioids (per day added)				-0.111	-0.371	0.150	0.40
Duration of treatment with benzodiazepines (per day added)				0.304	0.064	0.544	0.013
Duration of treatment with hypnotics (per day added)				0.042	-0.226	0.310	0.76
Duration of treatment with α2-agonists (per day added)				-0.200	-0.446	0.046	0.11

PeLOD = Paediatric Logistic Organ Dysfunction score; PICU = paediatric intensive care unit; PIM3 = Paediatric Index of Mortality 3 score; PN = parenteral nutrition.
For externalising problems as reported by parents, higher scores reflect worse performance.

[a] Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[b] A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2).

[c] Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.

[d] Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.

[e] Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[182]

[f] The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).

[g] The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S1-6: Multivariable linear regression analyses determining significant and independent associations between risk factors and visual-motor integration at 2 years' follow-up within the tested patient population

	Model adjusted for risk factors				Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Randomisation to late vs. early initiation of PN	***0.468***	***0.087***	***0.850***	***0.016***	***0.422***	***0.037***	***0.807***	***0.031***
Centre								
Leuven vs. Edmonton	5.647	3.729	7.566	<0.0001	5.449	3.506	7.391	<0.0001
Rotterdam vs. Edmonton	4.879	3.032	6.727	<0.0001	4.834	2.961	6.708	<0.0001
Male vs. female sex	-0.789	-1.178	-0.400	<0.0001	-0.794	-1.185	-0.403	<0.0001
Right vs. left hand preference	0.544	-0.091	1.179	0.092	0.542	-0.101	1.185	0.098
Medium vs. high STRONGkids risk level[a]	0.339	-0.334	1.013	0.32	0.270	-0.417	0.958	0.44
Diagnostic category (as compared with Cardiac surgery)								
Surgical								
Abdominal	0.449	-0.358	1.255	0.27	0.372	-0.436	1.180	0.36
Burns	0.585	-3.065	4.235	0.75	1.054	-2.699	4.807	0.58
Neurosurgery - traumatic brain injury	-0.037	-0.786	0.713	0.92	0.031	-0.717	0.778	0.93
Thoracic	0.630	-0.273	1.533	0.17	0.528	-0.380	1.436	0.25
Transplantation	-1.738	-3.224	-0.253	0.021	-1.099	-2.725	0.527	0.18
Orthopaedic surgery-trauma	-2.207	-3.346	-1.069	0.00015	-2.236	-3.378	-1.094	0.00013
Other	0.245	-0.849	1.340	0.65	0.289	-0.817	1.395	0.60
Medical								
Cardiac	0.128	-1.022	1.277	0.82	0.333	-0.894	1.560	0.59
Gastrointestinal-hepatic	0.245	-2.770	3.260	0.87	0.239	-2.761	3.239	0.87
Haematologic-oncologic	1.275	-0.776	3.326	0.22	1.891	-0.263	4.045	0.085
Neurologic	-0.472	-1.371	0.427	0.30	-0.268	-1.189	0.652	0.56
Respiratory	0.506	-0.233	1.246	0.17	0.445	-0.315	1.206	0.25
Other	-0.180	-1.188	0.827	0.72	-0.279	-1.324	0.767	0.60

Table S1-6 continued

	Model adjusted for risk factors				Model further adjusted for acute effects of Late-PN vs Early-PN and for post-randomisation treatments			
Variable	**Beta-estimate**	**Confidence interval**		**P-value**	**Beta-estimate**	**Confidence interval**		**P-value**
Infant (age<1y) vs. child at randomisation	1.228	0.799	1.657	<0.0001	1.179	0.736	1.622	<0.0001
Malignancy vs. no malignancy	0.014	-0.945	0.972	0.97	0.196	-0.771	1.163	0.69
Diabetes vs. no diabetes	0.511	-4.802	5.823	0.85	-0.090	-5.383	5.204	0.97
Syndrome vs. no syndrome[b]	-1.336	-1.985	-0.687	<0.0001	-1.474	-2.125	-0.823	<0.0001
PIM3 score (per point added)[c]	0.017	-0.169	0.203	0.85	0.028	-0.163	0.219	0.77
PeLOD score first 24 hrs (per point added)[d]	-0.015	-0.039	0.010	0.23	-0.012	-0.037	0.013	0.34
Known non-European origin vs. other[e]	-0.144	-0.901	0.613	0.70	-0.133	-0.888	0.622	0.72
Known non-Caucasian vs. other[e]	-0.278	-1.197	0.642	0.55	-0.333	-1.250	0.585	0.47
Known not exclusive Dutch or English language vs. other	0.350	-0.231	0.932	0.23	0.381	-0.201	0.962	0.19
Socioeconomic status								
Educational level parents (as compared with level 1)[f]								
Educational level 1.5	0.121	-1.036	1.279	0.83	0.029	-1.143	1.201	0.96
Educational level 2	0.500	-0.469	1.469	0.31	0.413	-0.565	1.391	0.40
Educational level 2.5	0.419	-0.614	1.451	0.42	0.319	-0.717	1.355	0.54
Educational level 3	0.988	-0.062	2.037	0.062	0.883	-0.173	1.939	0.10
Educational level unknown	0.235	-0.769	1.238	0.64	0.080	-0.931	1.091	0.87
Occupational level parents (as compared with level 1)[g]								
Occupational level 1.5	0.643	-1.186	2.472	0.49	0.807	-1.015	2.630	0.38
Occupational level 2	0.687	-1.140	2.515	0.46	0.808	-1.016	2.631	0.38
Occupational level 2.5	0.899	-0.990	2.789	0.35	1.075	-0.812	2.961	0.26
Occupational level 3	1.079	-0.766	2.924	0.25	1.228	-0.610	3.065	0.19
Occupational level 3.5	0.669	-1.295	2.634	0.50	0.766	-1.193	2.725	0.44
Occupational level 4	0.392	-1.520	2.304	0.68	0.625	-1.286	2.536	0.52
Occupational level unknown	0.506	-1.314	2.327	0.58	0.619	-1.196	2.434	0.50

Table S1-6 continued

Parental smoking between birth and PICU admission vs. no smoking	-0.247	-0.729	0.235	0.31	-0.293	-0.765	0.180	0.22
New infection vs. no new infection					0.043	-0.672	0.759	0.90
Duration of stay in the PICU (per day added)					-0.026	-0.089	0.037	0.41
Days with hypoglycaemic event (per day added)					0.256	-0.175	0.687	0.24
Duration of mechanical ventilatory support (per day added)					0.026	-0.015	0.068	0.21
Duration of treatment with antibiotics (per day added)					0.027	-0.033	0.086	0.37
Duration of haemodynamic support (per day added)					-0.025	-0.068	0.019	0.26
Duration of treatment with corticosteroids (per day added)					-0.078	-0.148	-0.007	0.030
Duration of treatment with opioids (per day added)					0.022	-0.039	0.084	0.47
Duration of treatment with benzodiazepines (per day added)					-0.035	-0.093	0.022	0.22
Duration of treatment with hypnotics (per day added)					-0.053	-0.118	0.011	0.10
Duration of treatment with $\alpha 2$-agonists (per day added)					0.078	0.021	0.134	0.0074

PeLOD = Paediatric Logistic Organ Dysfunction score; PICU= paediatric intensive care unit; PIM3 = Paediatric Index of Mortality 3 score; PN = parenteral nutrition.
For visual-motor integration, higher scores reflect better performance.

[a] Scores on the Screening Tool for Risk on Nutritional Status and Growth (STRONGkids) range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[b] A prerandomisation syndrome or illness a priori defined as affecting or possibly affecting neurocognitive development (Methods_S2).

[c] Paediatric Index of Mortality 3 (PIM3) scores, with higher scores indicating a higher risk of mortality.

[d] Paediatric Logistic Organ Dysfunction (PeLOD) scores range from 0 to 71, with higher scores indicating more severe illness.

[e] Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[182]

[f] The education level is the average of the paternal and maternal educational level, and calculated based upon the 3-point scale subdivisions as made by the Algemene Directie Statistiek (Belgium; statbel.fgov.be/nl/) and the Centraal Bureau voor de Statistiek (The Netherlands; statline.cbs.nl): Low (=1), middle (=2) and high (=3) educational level (Methods_S1).

[g] The occupation level is the average of the paternal and maternal occupation level, which is calculated based upon the International Isco System 4-point scale for professions (Methods_S1).http://www.ilo.org/public/english/bureau/stat/isco/.

Table S2: Comparison of patients randomised to late parenteral nutrition during PICU stay with healthy control children for the tests significantly affected by the randomised intervention

Neurocognitive function	P-value
Visual-motor integration	0.00052
Externalising problems as reported by parents/caregivers	0.34
Inhibition as reported by parents/caregivers	0.66
Working memory as reported by parents/caregivers	0.032
Meta-cognition index as reported by parents/caregivers	0.34
Overall executive functioning as reported by parents/caregivers	0.12

Table S3: Impact of late versus early parenteral nutrition in infants for tests showing a significant interaction P-value with age group

Variable	Beta-estimate	Confidence interval		P-value
Overall executive functioning	-3.843	-6.361	-1.325	0.0029
Meta-cognition	-3.749	-6.244	-1.254	0.0034
Working memory	-3.594	-6.052	-1.135	0.0043

Chapter 7

Cost-Effectiveness Study of Early versus Late Parenteral Nutrition in Critically Ill Children (PEPaNIC): Preplanned Secondary Analysis of a Multicentre Randomised Controlled Trial

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ABSTRACT

Background

The multicentre randomised controlled PEPaNIC trial showed that withholding parenteral nutrition (PN) during the first week of critical illness in children was clinically superior to providing PN early. This study describes the cost-effectiveness of this new nutritional strategy.

Methods

Direct medical costs were calculated with use of a micro-costing approach. We compared the costs of late versus early initiation of PN (n=673 versus n=670) in the Belgian and Dutch study populations from a hospital perspective, with use of student's *t* test with bootstrapping. Main cost drivers were identified and the impact of new infections on the total costs was assessed.

Results

Mean direct medical costs for patients receiving Late-PN (€26.680, IQR €10.090-€28.830 per patient) were 21% lower (€-7.180, p=0.007) than for patients receiving Early-PN (€33.860, IQR €11.080-€34.720). Since late PN was more effective and less costly, this strategy was superior to early PN. The lower costs for PN only contributed for 2.1% to the total cost reduction. The main cost driver was intensive care hospitalisation costs (€-4.120, p=0.003). The patients who acquired a new infection (14%) were responsible for 41% of the total costs. Sensitivity analyses confirmed consistency across both healthcare systems.

Conclusions

Late initiation of PN decreased the direct medical costs for hospitalisation in critically ill children, beyond the expected lower costs for withholding PN. Avoiding new infections by late initiation of PN yielded a large cost reduction. Hence, late initiation of PN was superior to early initiation of PN largely via its effect on new infections.

BACKGROUND

Healthcare costs are growing worldwide. Intensive care is responsible for a substantial proportion of all healthcare expenses, particularly prolonged intensive care and palliative care.[98,193-195] Intensive care costs are largely dependent on length of stay (LOS) in the paediatric intensive care unit (PICU), which is strongly influenced by complications, such as hospital-acquired infections.[196]

Recently, a multicentre, randomised, controlled, parallel-group, superiority trial, with the acronym PEPaNIC (n=1440) concluded that withholding parenteral nutrition (PN) during the first week of critical illness in children was clinically superior to providing PN within 24 hours when enteral nutrition was insufficient,[18] resulting in fewer patients with new infections. Aside from this clinical benefit, an additional economic benefit of late initiation of PN would be an extra argument for implementation of this new nutritional strategy.

Currently, no studies have investigated costs of different timing of initiation of PN in children in the paediatric intensive care unit (PICU). Our cost-effectiveness analysis was predesigned, offering a unique opportunity for a micro-costing approach.[197] With this method of calculating hospital costs, all relevant cost categories are included and costs are calculated at the most detailed level per patient, in contrast to the gross-costing approach, whereby the cost categories are highly aggregated or only hospitalisation costs are included.

We hypothesised that withholding PN for one week is a cost saving strategy comprising more than merely omitting the costs of PN itself. The aims of this study were: 1) to compare total direct medical costs of early versus late initiation of PN in the PICU from a hospital perspective in an international context; 2) to provide a detailed insight into the distribution of cost components; and 3) to assess the impact of acquiring a new infection in the PICU on direct medical costs.

METHODS

Context

A total of 1440 critically ill children, aged 0 (term neonates) to 17 years, from three large tertiary referral PICUs in three countries (University Hospitals Leuven in Belgium, Erasmus MC-Sophia Children's Hospital in The Netherlands, and Stollery Children's Hospital in Canada) were randomly assigned to early initiation of PN (standard care) or late initiation of PN (intervention). Initiation and dose of enteral nutrition (EN) and the administration of trace elements, minerals and vitamins were identical in both groups. Patients assigned to the group with Late-PN (n=717) received no PN during the first week of critical illness. Patients assigned to the group with Early-PN (n=723) received PN within 24 hours, according to the local standards. After the first week, when patients were still in the PICU and EN was insufficient to meet nutritional goals, PN was administered equally in both groups according to standard nutrition protocols.[18,129] The institutional ethical review boards of the participating centres in Leuven (ML8052), Rotterdam (NL38772.000.12) and Edmonton (Pro00038098) approved the

study, which was performed in accordance with the 1964 Declaration of Helsinki and its amendments. Written informed consent was obtained from the parents or legal guardians.

In this study, we explored the total direct medical costs, from a hospital perspective, in the Belgian and Dutch study populations, as these healthcare systems are reasonably comparable. Including the patients from Canada would introduce a bias, as cost calculations and reimbursements are too differently structured in Anglo-Saxon healthcare systems. Therefore, we excluded this centre from the cost analyses.

Healthcare systems

In the Dutch healthcare system, hospitals are mainly paid by private insurance companies according to tariffs based on "Diagnosis Therapy Combination" (DBC).[198] However, registered DBCs per patient do not represent individualised healthcare consumption. As the tariffs are fixed, specific healthcare activities are not presented in the patients' invoices. Therefore, we used individual healthcare consumption and corresponding unit prices, which are registered by the hospital for reporting and stock management.

In Belgium, healthcare costs are reimbursed by sickness funds and private insurance companies. Since all healthcare activities are represented in the patients' invoices, these invoices can be used to accurately quantify healthcare consumption. However, total healthcare costs are mainly covered by advance payments to the hospital, directly by the government. Consequently, for healthcare activities for which the hospital receives these in advance payments, only 25% of the costs are represented in the patients' invoices. When this is corrected to 100%, they reflect real healthcare costs from a hospital perspective.[199]

Resource consumption

The participating clinicians filled out standardised case report forms during PICU stay, including duration of PICU dependency, post-PICU hospitalisation, mechanical ventilation, renal replacement therapy (RRT) and mechanical hemodynamic support. LOS encompassed both index and transferral hospitals. PN consumption was obtained from the study database for Dutch patients and from the invoices for Belgian patients. Detailed information on diagnostic procedures, medication, blood products, surgery and consultations were obtained from the data management system of the hospital for Dutch patients and from the invoices for Belgian patients.

Healthcare consumption was divided into ten cost categories: 1) PICU hospitalisation (both index and transferral hospital); 2) post-PICU hospitalisation (both index and transferral hospital); 3) PN; 4) medication; 5) laboratory diagnostics; 6) other diagnostics; 7) ventilator support; 8) RRT and mechanical haemodynamic support; 9) surgery; and 10) consultations from other specialists.

Economic evaluation

The cost-effectiveness analyses were based on the Dutch and Belgian guidelines for performing costs studies.[199,200] Furthermore, this study is in line with the international

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[201] Real medical costs were calculated by multiplying the volumes of healthcare use with the corresponding unit prices. Costs were calculated during two periods. From randomisation until ready-for-discharge from PICU, or death, the costs in all aforementioned cost categories were calculated. Ready-for-discharge was a priori chosen to avoid bias due to availability of beds on regular wards and was defined as "no longer requiring or no longer at risk for requiring vital organ support". From ready-for-discharge from PICU until discharge from hospital, only hospitalisation costs were calculated. If a patient was transferred to another hospital, only hospitalisation costs were included for the period from discharge from the index hospital until discharge from the transferral hospital or death. Since the time horizon was less than one year, unit prices were not discounted.

In the Netherlands, the unit prices were available from the hospital's financial database, and were adjusted to the year 2014. For hospital days (non-PICU), a national guiding price per day was used, because children were referred to different hospitals, charging different prices.[200] The daily costs of mechanical ventilation and RRT were estimated based on published literature.[202,203] Production costs of infusions for the intervention group were calculated by summing the costs of the PN ingredients, pharmacy compounding costs, and additional trial intervention costs.

In Belgium, financial data were registered by the billing and warehousing collaborators of the index hospital as this is standard procedure for invoicing. The unit prices were official, nationally fixed prices adjusted to the year 2014, and were converted to 100%, if necessary, to obtain real costs from a hospital perspective.[199] There were no additional trial intervention costs for infusions in the group receiving late initiation of PN.

Costs of medication were categorised according to the first level of the Anatomical Therapeutic Chemical (ATC) classification, which is the World Health Organisation (WHO) tool for drug utilisation research.[204] Each drug has its unique ATC code and price. Costs for ATC code B05BA (PN solutions) were reported separately. Since we were unable to distinguish costs per ATC code in Dutch patients, we excluded them from this ATC code analysis. However, since new infections were a primary outcome in the trial, we analysed the costs of anti-infective drugs in both centres.

Study endpoints

The primary endpoint was the difference in total direct medical costs, from a hospital perspective, between early and late initiation of PN. Furthermore, the ten cost categories were analysed separately. In order to give insight into costs among different groups of patients, we compared total direct medical costs of Early-PN with Late-PN in the stratification groups as used for the PEPaNIC trial: "Surgical cardiac", "Surgical other", "Medical neurological" and "Medical other", and age groups younger and older than one year [129]. Additionally, the drugs responsible for differences in medication costs were investigated based on the ATC codes. Also, the impact of new infections on total costs was calculated.

Finally, we explored the cost-effectiveness of Late-PN, using the number of patients with a new infection prevented in the PICU as an effect measure.

Statistical analyses

The PEPaNIC trial was a priori statistically powered to detect a difference in new infections. Therefore, the statistical power to detect differences in total direct medical costs was dependent on the number of patients enrolled in the original PEPaNIC trial. This cost analysis was an a priori planned secondary analysis.

Costs were reported in euro (€), as mean (SD and IQR), as recommended for cost analyses.[205] IQR was reported, as cost data is always highly skewed, and IQR reflects the statistical dispersion more realistically than standard deviation or standard error. Other data were reported as mean (SE), median (IQR) or number (%), as appropriate. In order to check whether the major costs were similarly distributed into the cost categories in both centres, a Pareto analysis was performed. This is a chart to demonstrate which factors are contributing most to a problem (i.e. total costs).[206]

Costs were compared univariably by using Student's one-tailed *t* test with bootstrapping (x1000),[205] LOS was compared using the Mann-Whitney U test, and the incidence of new infection was compared using Fisher's exact test. Based on the clinical results that point out clearly that late PN reduces resource consumption by reduction of new infections and shorter PICU stay, we have chosen to test the differences in costs one-sided, hypothesising that Late-PN is less costly than Early-PN. One-sided p-values <0.05 were considered statistically significant. Effects were reported as mean difference or odds ratio (OR) with the corresponding 95% confidence interval (CI). The OR for acquiring a new infection was adjusted for age, risk of malnutrition (STRONGkids group), treatment centre, admission diagnosis, and degree of organ failure (PeLOD score), in line with the PEPaNIC trial[18] and also PIM2 score to adjust for risk of mortality. The adjusted OR was analysed using binary logistic regression. Analyses were conducted using IBM SPSS statistics, version 24.0.

Sensitivity analyses

Sensitivity analyses were conducted as follows:

1. The total costs were analysed using prices from the Belgian healthcare system for all patients.
2. The total costs were analysed using prices from the Dutch healthcare system for all patients.
3. The total costs were analysed separately in the Belgian patients.
4. The total costs were analysed separately in the Dutch patients.
5. As only the hospitalisation costs of the post-PICU period were included in the primary analysis, the additional post-PICU costs (i.e. laboratory, medication costs) were left out. Since this could underestimate our results, the estimated additional post-PICU costs were added in the third sensitivity analysis. These additional post-PICU costs were estimated based on the invoices of the Belgian patients

RESULTS

We compared the total direct medical costs of Late-PN (n=673 patients) with those of early-PN (n=670 patients) in the Dutch and Belgian study populations. The patients' baseline characteristics and main clinical outcomes are described in Table 1.

Total healthcare costs and evaluation of cost drivers

Late-PN, as compared with Early-PN, reduced the mean total direct medical costs by €7.180 (95%CI [€-12.920;€-1.880], p=0.007) per patient (Early-PN €33.860, Late-PN €26.680), which is a saving of 21% (Table 2).

The major costs were divided into cost categories similarly for both centres (Appendix). Differences in mean costs between Belgian and Dutch patients were due to shorter duration of stay in PICU (factor 0.55) in Belgian patients (p<0.001), which might be caused by differences in patient populations. In contrast, the Belgian costs per day in PICU (mean costs of all categories summed, except hospitalisation costs post-PICU, divided by the duration of PICU stay) were higher (factor 1.18) than the Dutch costs (p<0.001). Almost all cost categories showed lower costs with Late-PN than with Early-PN. The largest reduction was found in PICU hospitalisation costs (€-4.120, 95%CI [€-7.590; €-1.500]), medication costs (€-650, 95%CI [€-1.360;€100]), and ventilator support costs (€-640, 95%CI [€-1.260;€-190]) (Table 2). This reduction in costs is in line with the shorter PICU stay in the Late-PN group (Table 1). PN costs were responsible for 2.1% (-€150, 95%CI [€-200;€-110]) of the reduction in total costs.

Table 1: Baseline characteristics and main clinical outcomes

	Early-PN (n=670)	Late-PN (n=673)	
Baseline characteristic[a]			
Median age (IQR) - years	1.3 (0.3-6.0)	1.4 (0.2-7.0)	
Age <1 year	311 (46.4)	312 (46.4)	
Male sex	386 (57.6)	393 (58.4)	
STRONGkids risk level[b]			
Medium	593 (88.5)	600 (89.2)	
High	77 (11.5)	73 (10.8)	
Median PeLOD score, first 24 hour in PICU (IQR)[c]	21 (12-32)	21 (11-31)	
Median PIM2 score (IQR)[d]	-2.8 (-3.7;-1.3)	-2.8 (-3.7;-1.6)	
Emergency admission	325 (48.5)	308 (45.7)	
Diagnostic group			
Surgical cardiac	264 (39.4)	259 (38.5)	
Surgical other	202 (30.1)	205 (30.4)	
Medical neurological	44 (6.6)	50 (7.4)	
Medical other	160 (23.9)	159 (23.5)	
Condition on admission			
Mechanical ventilation required	596 (90.0)	587 (87.2)	
ECMO or other mechanical hemodynamic support required	16 (2.4)	22 (3.3)	
Infection	256 (38.2)	244 (36.3)	
Clinical primary outcome			**P-value**[e]
New infections - No. (%)	120 (17.9)	71 (10.6)	<0.001
Median duration of stay in PICU (IQR) – days[e]	4 (2-9)	3 (2-7)	0.002

ECMO = extracorporeal membrane oxygenation, PeLOD = Paediatric Logistic Organ Dysfunction, PIM2 = Paediatric Index of Mortality 2, PICU = paediatric intensive care unit, PN = parenteral nutrition, STRONGkids = Screening Tool for Risk on Nutritional Status and Growth.

[a]There were no significant differences in characteristics between treatment groups at baseline.

[b]STRONGkids scores range from 0 to 5, with a score of 0 indicating a low risk of malnutrition, a score of 1 to 3 indicating medium risk, and a score of 4 to 5 indicating high risk.

[c]PeLOD scores range from 0 to 71, with higher scores indicating more severe illness.

[d]PIM2 scores, with higher scores indicating a higher risk of mortality.

[e]The duration of stay in the PICU was defined as the time from admission until the patient was ready for discharge (i.e., the patient no longer required or was no longer at risk for requiring vital-organ support). The duration of stay was not censored, nor adjusted for death.

Table 2: Healthcare costs split by major cost categories

Cost category	Early-PN, €			Late-PN, €			Mean difference [95% CI], €	P-value (*t* test)
	Mean	SD	p25-p75	Mean	SD	p25-p75		
PICU hospitalisation	13.710	35.130	2.270-13.250	9.590	16.730	2.270-9.070	-4.120 [-7.590;-1.500]	0.003
Medication	1.810	7.430	250-1000	1.160	3.080	220-830	-650 [-1.360;100]	0.03
Ventilator support	1.740	6.650	150-1.430	1.100	2.300	150-1.070	-640 [-1.260;-190]	0.03
Post-PICU hospitalisation	7.140	14.530	1.500-6.900	6.560	14.270	1.500-6.270	-580 [-2.100;1.080]	0.24
Surgery	4.760	5.480	280-6.500	4.240	4.260	200-6.280	-520 [-1.080;10]	0.03
Laboratory diagnostics	2.290	4.090	540-2.160	1.820	3.370	440-1.820	-460 [-860;-40]	0.01
PN	300	500	60-300	150	270	20-170	-150 [-200;-110]	<0.001
Other diagnostics	690	2.020	80-550	610	1.610	80-430	-80 [-290;-110]	0.20
Consultations	470	690	40-680	440	630	30-680	-30 [-100;50]	0.19
RRT and mechanical hemodynamic support	950	6.740	0-0	1.010	9.370	0-0	60 [-810;1.020]	0.45
Total	33.860	57.610	11.080-34.720	26.680	35.850	10.090-28.830	-7.180 [-12.920;-1.880]	0.007

Cost categories were ranked according to the mean difference between the treatment groups.

CI = confidence interval, PICU = paediatric intensive care unit, PN = parenteral nutrition, RRT = renal replacement therapy.

The age category (<1 year versus ≥1 year) was not apparently related to proportional cost reduction with late initiation of PN (Appendix). Patients admitted for a medical reason other than neurological disease had the largest cost reduction with Late-PN (€-14.720, 95%CI [€-30.720;€130], p=0.04) (Appendix). Patients admitted for non-cardiac surgery also had cost reduction with Late-PN (€-9.490, 95%CI [€-20.720;€1.040], p=0.05) (Appendix). Furthermore, 26% of the patients had a prolonged PICU stay (>7 days), accounting for 60% of the costs. Moreover, the most expensive 1% of patients accounted for 13% of the total costs.

The distribution of medication costs is described in Table 3. The combination of medications of category B (blood and blood forming organs), containing PN solutions, and category J (anti-infectives), containing antibiotics, was responsible for 80% of the reduction in medication costs with Late-PN (Table 3)

Table 3: Medication costs of Belgian patients split by Anatomical Therapeutic Classification system classes

ATC code	Early-PN, €			Late-PN, €			Mean difference [95%CI], €	P-value (*t* test)
	Mean	SD	p25-p75	Mean	SD	p25-p75		
B (blood/blood forming organs)	850	1.820	210-740	580	1.350	140-480	-270 [-510;-40]	0.02
J (anti-infectives)[a]	320	2500	4-90	170	1.030	4-50	-150 [-470;80]	0.17
A (alimentary tract/metabolism)	70	250	20-70	50	80	10-40	-30 [-40;-10]	<0.001
V (various)	100	140	20-140	80	110	20-110	-20 [-40;-7]	0.004
N (nervous system)	90	180	30-80	70	150	30-80	-20 [-40;0]	0.03
C (cardiovascular)	55	150	3-50	45	100	1-50	-10 [-30;5]	0.07
R (respiratory)	20	150	0-0	10	50	0-0	-10 [-30;7]	0.10
H (hormonal)	30	110	0-30	20	60	0-30	-10 [-20;3]	0.10
M (musculo-skeletal)	13	40	3-10	7	10	3-9	-5 [-10;-2]	0.01
D (dermatologics)	10	70	0-8	7	30	0-8	-3 [-10;3]	0.26
S (sensory organs)	3	5	0-4	2	3	0-4	-1 [-1;0]	0.01
P (antiparasitic)	1	20	0-0	0	0	0-0	1 [-3;0]	0.19
G (genito-urinary / sex hormones)	1	8	0-0	1	8	0-0	0 [-1;1]	0.48
L (antineoplasmic / immunomodulating)	25	330	0-0	45	320	0-0	20 [-30;60]	0.26
Total	1.600	4.663	380-1.260	1.070	2.577	310-830	-500 [-1.060;20]	0.03

Cost categories were ranked according to the mean difference between the treatment groups.

CI = confidence interval, PN = parenteral nutrition.

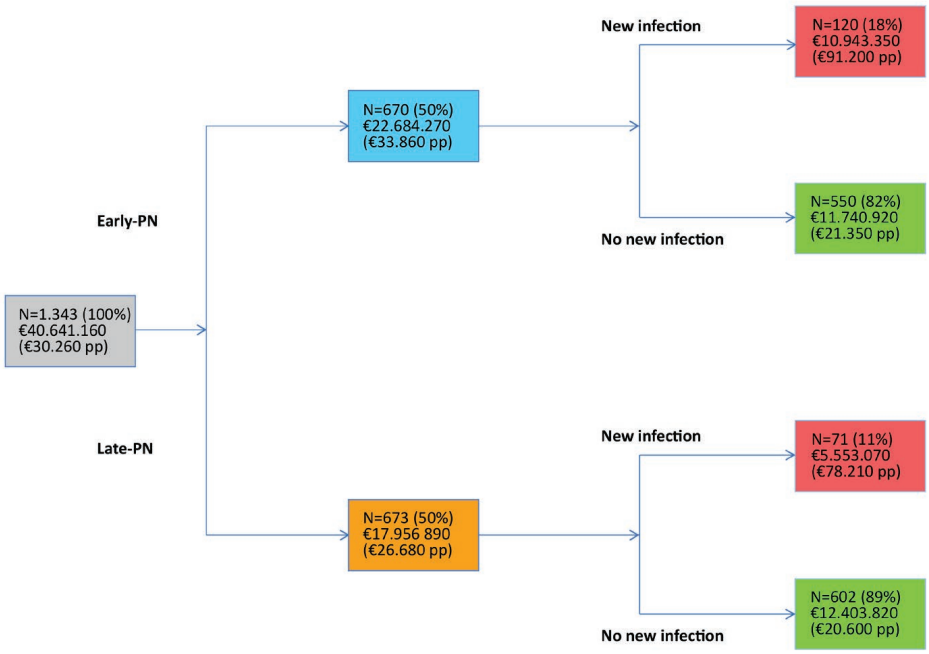
[a]Data from both Belgian and Dutch patients.

Impact of new infections

The proportion of patients with a new infection acquired in the PICU was smaller with Late-PN than with Early-PN (patients included for cost analysis: 10.6% and 17.9%, respectively, p<0.001; Table 1), with a corresponding adjusted odds ratio of 0.51 (95%CI [0.36;0.71]). In the whole group, 1.2% of the least expensive 50% of patients had acquired a new infection compared to 28.5% of the most expensive 50% of patients. Moreover, 85% (11 patients) of the most expensive 1% of patients (13 patients) had acquired a new infection. Figure 1 depicts the cost tree of patients with and without a new infection in both randomisation groups. In patients who acquired a new infection, costs were increased from €21.350 to €91.200 (difference €69.850, 95%CI [€50.700;€91.560], p=0.001) with Early-PN and from €20.600 to €78.210 (difference €57.610, 95%CI [€41.890;€73.970], p=0.001) with Late-PN, predominantly caused by PICU hospitalisation costs (Early-PN group: difference €37.210, 95%CI [€26.200;€52.750], p=0.002; Late-PN group: difference €27.530, 95%CI [€20.660;€34.940], p=0.001).

Late-PN was more effective and less costly than Early-PN, and falls into the south-eastern quadrant of the cost-effectiveness plane. Interventions in this quadrant are always considered cost-effective.[207,208]

Figure 1: Costs of patients with or without new infections



PN = parenteral nutrition, pp = per patient.

Sensitivity analyses

The primary results were robust, as they could be reproduced with multiple sensitivity analyses (Table 4). Using the Dutch or Belgian unit prices for all patients showed a cost difference of late versus early PN of €-8.690 resp. €-6.090, which is within the 95%CI of the primary analysis of the base case ([€-12.920;€-1.880). Also, when analysing the Dutch and Belgian patients separately, the cost reduction with late PN was within the 95%CI of the primary analysis of the base case (Table 4). The difference in absolute costs between the centres was predominantly due to more resource consumption in the Dutch patients (i.e. longer LOS) (Appendix). In the third sensitivity analysis, total post-PICU costs were estimated and added to the total PICU costs. Post-PICU costs were predominantly hospitalisation costs (85%), which were already included in the base case. Consequently, the additional post-PICU costs of approximately €1.100 in this sensitivity analysis represented the 15% of post-PICU costs that were not included in the base case.

DISCUSSION

This cost-effectiveness study of the PEPaNIC trial showed that the total direct medical costs were considerably lower when PN was withheld during the first week of critical illness in children as compared with early initiation of PN. This cost reduction was mainly due to a lowering of PICU hospitalisation costs, although most cost components were reduced by not using Early-PN. The reduction of the costs for PN was responsible for only 2.1% of the total cutback of costs, which supported our hypothesis that the health-economic impact of withholding PN encompassed more than the omission of costs for PN itself. Taking into account the beneficial clinical impact of Late-PN, we can conclude that withholding PN in the first week of critical illness is superior to Early-PN largely by preventing new infections which is cost-saving.[207,208]

Our results confirmed previously published results of studies in critically ill adults that have compared early with Late-PN.[123,127] The American Thoracic Society has included "withholding PN for one week in critically ill adults" in the top five recommendations to improve healthcare while reducing healthcare costs.[209] One other cost analysis of the timing of PN in adults identified no difference in LOS, and US$ 3.170 higher costs per patient with late initiation of PN. However, the estimated costs in this study were based on a Monte Carlo simulation, in which the estimated probabilities of events, such as mechanical ventilation, have a large impact on cost differences.[210] A micro-costing approach, used in our study, provides more precise and more reliable results, as this method uses the real costs that have been incurred.

Three studies of PICU costs have been previously published, which allow a comparison with our study results. First, Harron et al. reported PICU stay and direct PICU costs that are comparable to those we reported here, which supports the generalisability of the findings of our study.[211] Second, the CHiP study reported hospital costs during a 12-month period (£21.000)[98] that were slightly lower than those found in our study. These differences could be explained by different study populations, with more patients included after cardiac surgery, which may incur lower costs than medical or non-cardiac surgical PICU patients, and more patients with less organ failure, reflected by mean PeLOD of 7.5 as compared with a median PeLOD of 21 in our study. Third, Morillo-García et al. reported higher costs for children with a nosocomial infection, as compared with those without a new infection,[96] which supports our conclusion that healthcare costs can be reduced by preventing new infections. In line with previous research,[212] we observed that the duration of PICU stay had a major effect on the costs. This was also reflected in the finding that patients with a prolonged PICU stay, the minority of the total patient population that was included, accounted for the majority of the costs.

Table 4: Sensitivity analyses

Analysis	Early-PN, €				Late-PN, €				Mean difference [95%CI], €	P-value (*t* test)
	n	Mean	SD	p25-p75	n	Mean	SD	p25-p75		
Primary analysis										
Total PICU costs and post-PICU hospitalisation costs	670	33.860	57.600	11.080-34.720	673	26.680	35.850	10.090-28.830	-7.180 [-12.920;-1.880]	0.007
Sensitivity analysis										
1. Belgian unit prices[a]	670	28.380	41.210	10.460-29.880	673	22.290	24.960	9.320-25.390	-6.090 [-9.950;-2.480]	<0.001
2. Dutch unit prices[b]	670	37.960	62.120	12.570-38.350	673	29.270	37.180	11.560-32.390	-8.690 [-14.090;-3.190]	0.003
3. Belgian patients	373	22.930	22.460	10.060-23.780	377	17.600	15.920	9.150-19.700	-5.330 [-8.650;-2.360]	0.003
4. Dutch patients	297	47.580	78.820	14.860-46.410	296	38.250	48.630	12.790-42.380	-9.330 [-20.410;1.250]	0.04
5. Total PICU and total post-PICU costs[c]	670	34.990	58.316	11.470-35.580	673	27.800	36.859	10.530-30.580	-7.190 [-12.420;-1.970]	0.002

CI = confidence interval, PICU = paediatric intensive care unit, PN = parenteral nutrition.

[a]The total costs were analysed with the use of prices from the Belgian healthcare system for all patients.

[b]The total costs were analysed with the use of prices from the Dutch healthcare system for all patients.

[c]In the primary analysis, only the hospitalisation costs of the post-PICU period were included. The estimated additional post-PICU costs (i.e. laboratory, medication) were added. These additional post-PICU costs were estimated based on the invoices of the Belgian patients.

The reduction in medication costs with Late-PN versus Early-PN was mainly due to lower use of products in ATC categories B (blood and blood-forming organs) and J (anti-infectives). This corroborates the finding that Late-PN reduced the proportion of patients with new infections, as it also does in adults.[127] Additionally, patients with a new infection had higher total costs per patient than those without a new infection. The fact that the proportion of patients with new infections increased from 1.2% among the least expensive patients to 85% among the 1% most expensive patients pointed to an effect of new infections on the total costs. Therefore, reducing the number of PICU days by preventing the occurrence of new infections by Late-PN seems to have had most influence on the cost reduction.

The strength of this study is the micro-costing approach, reflecting real costs that incurred. Additionally, our findings appeared robust across two healthcare systems. We have carefully checked whether combining the Dutch and Belgian populations would compromise our results by performing sensitivity analyses, which have shown unanimously a cost reduction with Late-PN, which was well within the range of the confidence interval of the base case. These results may support that the international character of this study increased external validity and, possibly, applicability to other European countries.

Some limitations should also be addressed. First, the Dutch daily costs of mechanical ventilation and renal replacement therapy had to be estimated, based on published literature on PICU costs.[202,203] Second, the time horizon was limited to the hospital period and direct medical costs, and thus, the economic consequences could not be fully captured. One Swiss study, investigating out-of-pocket expenses of families with a child spending >4 days in PICU, reported mean 86 (±31) Franc (converted ~€137) per day, mainly on travel costs and meals.[213] As such, the full impact of Late-PN from a societal perspective could not be assessed. Third, quality-adjusted life years (QALYs) were not used as an outcome measure, as the time horizon was too short (hospital stay) to meaningfully assess long-term quality of life of critically ill children. It is acknowledged that a cost-utility analysis is preferred over a cost-effectiveness analysis, if a treatment has an impact on health-related quality of life. At this time, a long-term follow-up study is ongoing, with patients being evaluated 2 and 4 years after randomisation. This long-term follow-up study includes an assessment of quality of life. However, the aim of the current study was to perform a cost-effectiveness analysis and not a cost-utility analysis, which requires quality of life data. Finally, the lack of detailed drug costs for Dutch patients may have biased, and possibly underestimated, the differences in drug costs.

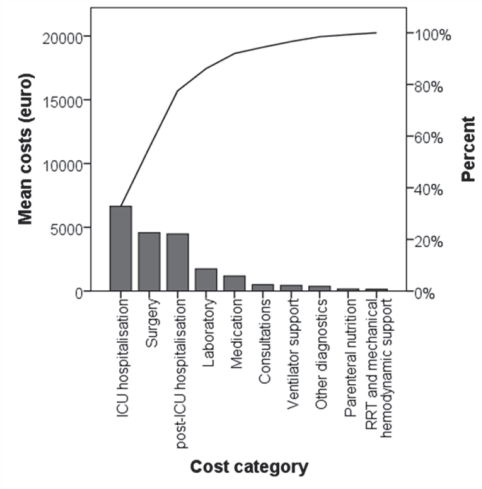
CONCLUSIONS

The cost analyses showed that Late-PN reduced the direct medical costs by 21% in critically ill children as compared with Early-PN, beyond the expected lower costs for the use of PN itself. Avoiding new infections by Late-PN yielded a large cost reduction. Withholding PN during the first week of critical illness in children can thus be recommended both from a clinical and a health-economic perspective.

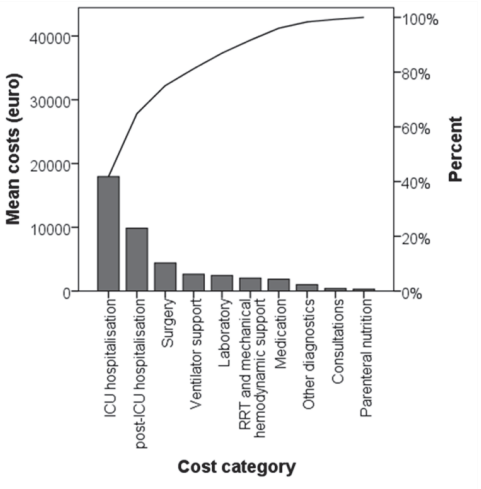
APPENDIX

Figure S1: Pareto charts of the cost categories

a. Belgian patients



b. Dutch patients



The continuous lines reflect the cumulative total costs.
ICU = intensive care unit, RRT = renal replacement therapy.

Table S1: Total healthcare costs split by age

Age group	Early-PN, €				Late-PN, €				Mean difference [95%CI], €	P-value (*t* test)
	n	Mean	SD	p25-p75	n	Mean	SD	p25-p75		
Age 0-1 year	311	39.240	69.030	12.580-38.980	312	30.700	38.790	12.000-31.130	-8.540 [-18.520;110]	0.04
Age ≥1 year	359	29.200	45.030	9.780-29.420	361	23.210	32.750	9.270-25.580	-5.990 [-12.040;-330]	0.02

Cost categories were ranked according to the mean difference between the treatment groups.

CI = confidence interval, PN = parenteral nutrition.

Table S2: Total healthcare costs split by diagnosis group

Diagnosis group	Early-PN, €				Late-PN, €				Mean difference [95%CI], €	P-value (*t* test)
	n	Mean	SD	p25-p75	n	Mean	SD	p25-p75		
Medical - Other	160	52.710	81.940	13.460-53.250	159	38.000	56.230	10.810-39.300	-14.710 [-30.720;130]	0.04
Surgery - Other	202	34.280	66.380	10.770-35.890	205	24.800	28.430	8.660-28.880	-9.480 [-20.720;-1.040]	0.05
Surgery - Cardiac	264	23.740	23.840	11.030-27.440	259	21.730	21.930	10.680-22.830	-2.010 [-5.850;1.730]	0.16
Medical - Neurological	44	24.030	26.000	7.470-25.800	50	24.090	31.090	7.630-29.520	+60 [-10.630;11.160	0.50

Cost categories were ranked according to the mean difference between the treatment groups.

CI = confidence interval, PN = parenteral nutrition.

Table S3: Resource utilisation and costs per centre.

Centre	Leuven, Belgium (n=673)	Rotterdam, The Netherlands (n=670)
Resource utilisation		
Duration PICU (days) – mean (SE)	5.9 (0.4)	10.8 (1.0)
Duration post-PICU (days) – mean (SE)	9.0 (0.7)	15.7 (1.2)
Duration ventilator support (days) – mean (SE)	3.7 (0.2)	7.4 (0.8)
Duration renal replacement therapy (days) – mean (SE)	0.2 (0.1)	0.4 (0.1)
Duration mechanical hemodynamic support (days) – mean (SE)	0.4 (0.1)	0.7 (0.2)
Costs		
PICU hospitalisation (euro) – mean (SD, IQR)	6.650 (11.110, 1.980-6.800)	17.950 (38.650, 3.310-18.220)
Post-PICU hospitalisation (euro) – mean (SD, IQR)	4.470 (9.220, 1.500-3.990)	9.860 (18.600, 1.880-11.600)
PN (euro) – mean (SD, IQR)	160 (350, 20-150)	300 (470, 100-300)
Medication (euro) – mean (SD, IQR)	1.180 (3.540, 300-850)	1.870 (7.560, 160-970)
Laboratory diagnostics (euro) – mean (SD, IQR)	1.740 (2.460, 610-1.770)	2.450 (4.900, 200-2.640)
Other diagnostics (euro) – mean (SD, IQR)	380 (590, 110-380)	990 (2.630, 0-760)
Ventilator support (euro) – mean (SD, IQR)	450 (690, 150-440)	2.640 (2.640, 710-2.490)
Renal replacement therapy and mechanical hemodynamic support (euro) – mean (SD, IQR)	150 (1460, 0-0)	2.050 (12.090, 0-0)
Surgery (euro) – mean (SD, IQR)	4.580 (3940, 1.230-6.230)	4.400 (5.920, 0-6.980)
Consultations (euro) – mean (SD, IQR)	500 (360, 180-710)	400 (900, 0-440)
Total (euro – mean (SD, IQR)	20.250 (22.550, 9.570-21.160)	42.920 (65.630, 13.580-43.380)

PICU = paediatric intensive care unit, PN = parenteral nutrition.

Chapter 8

General Discussion

"PRIMUM NON NOCERE" – Hippocrates, ±400 B.C.

This thesis provides insight into the short-term and long-term clinical and economic consequences of withholding parenteral nutrition (PN) during the first week in critically ill children. Based on previous studies[18,20,43,127] and concerns raised by nutritional experts,[71-75,166] the main hypotheses that we tested were as follows:
Withholding PN during the first week in critically ill children…

- is effective and safe in neonates and undernourished children (**Chapter 3 and 4)**;
- does not negatively affect nutritional status **(Chapter 5)**;
- is effective and safe in the long term **(Chapter 6)**;
- is a cost-saving strategy comprising more than merely omitting the costs of PN itself **(Chapter 7)**.

OUTCOME PARAMETERS

There is an ongoing debate about the definition of optimal nutrition in critically ill children. Questions concern the best timing, dose, and route of nutrition administration in relation to improved survival, recovery, growth, and development. Based on the current evidence there are still many uncertainties over how to achieve optimal nutrition in critically ill children. Measures of outcomes in nutritional research can be separated into surrogate outcomes and clinical outcomes **(Chapter 1)**. Currently, most recommendations from international guidelines are based on observational research or randomised controlled trials (RCTs) with surrogate outcomes, such as nitrogen balance.[74,99] Methodologically sound RCTs with clinical outcome measures, such as mortality, incidence of complications, duration of mechanical ventilation, stay on the paediatric intensive care unit (PICU), and hospital stay, are very scarce in this field (**Chapter 1)**.[69] While surrogate outcomes are important to unravel the mechanistic responses to a nutritional intervention, the effect of an intervention on a patient's recovery should be verified with use of clinically relevant outcomes, both in the short and long term. However, with low mortality rates <5% nowadays,[18,79] efforts to improve other clinical outcomes are of increasing interest. Critically ill children are at risk of acquiring brain damage during PICU stay, which could affect neurocognitive development.[214] These neurocognitive deficits might increase with age, as new functions rely on undamaged tissues – also known as 'growing into deficit' – which emphasizes the need for long-term assessment. As summarized in **Chapter 1**, PICU-survivors may suffer from significant and long-lasting problems,[168] which comprises worse physical development (among others worse growth, chronic kidney disease, and muscle weakness),[79-83] and neurocognitive developmental problems (such as lower academic performance, lower attention, worse memory and behavioural problems).[20,87,89-95] Furthermore, a literature review showed that children who have been critically ill had a lower health-related quality of life.[88] Children who were treated with neonatal extracorporeal membrane oxygenation had a significantly lower health-related quality of life at the age of 5 years, as reported by the mother and themselves.[89] It is likely that multiple factors contribute

to this long-term 'legacy', such as pre-existent morbidity, social factors, disease-related factors and treatments. Traditionally, long-term outcomes were presumed to be unmodifiable by treatments during PICU admission. However, tight glycaemic control has recently been shown to improve neurocognitive outcomes in critically ill children 4 years after PICU admission.[20] Children in whom blood glucose levels were controlled to fasting levels performed better on tests for motor coordination and cognitive flexibility than children in whom hyperglycaemia was tolerated.[20] The thyroid and somatotropic axes seemed to react on tight glycaemic control with a fasting response in these children, which was related to improved short-term outcomes.[59,60] Hence, a nutritional intervention that further induces this fasting response might further reduce the long-term burden of critical illness. Moreover, enhanced recovery and improved long-term outcomes could contribute to sustainable healthcare. After all, with increasing healthcare expenses nowadays, cost-effectiveness is an important outcome measure as well.

PARENTERAL NUTRITION IN THE ACUTE PHASE OF CRITICAL ILLNESS

In critically ill children, the caloric targets are often not reached due to a number of barriers to enteral nutrition (EN) in the PICU.[77] If nutritional targets cannot be reached with EN alone, or if it is expected that PN will be necessary, common practice worldwide is to supplement EN with parenteral nutrition (PN).[67] However, systematic reviews have shown that there is no solid scientific evidence for supplementing EN with PN in critically ill children.[68,69] With respect to clinical outcomes, recent findings provided new insights into the debate on timing of initiating PN in critically ill children.

Late versus early initiation of PN

A large, international RCT (the "PEPaNIC" trial), conducted by the PICUs of University Hospitals Leuven, Belgium; Erasmus-MC Sophia Children's Hospital, Rotterdam, The Netherlands; and Stollery Children's Hospital, Edmonton, Alberta, Canada, investigated the effects of withholding PN during the first week (Late-PN) as compared with initiating PN within 24 hours (Early-PN) to supplement insufficient EN. In contrast to clinical practices and observational studies, this RCT concluded that in a heterogeneous population of critically ill children, from term newborns to 17 years of age, macronutrient restriction by Late-PN is superior to providing full nutritional intake by Early-PN on the following outcome parameters: incidence of new infections, duration of PICU dependency and hospital stay, duration of mechanical ventilatory support, and need for renal replacement therapy.[18]

Despite these recent insights, about three-quarters of PICUs worldwide still administer PN to supplement EN during the first week, which shows that PN is still considered essential **(Chapter 2)**. Of notice was the low awareness among respondents of the results from the PEPaNIC study, although this was a large, international, randomised study, published in an open access, high-impact journal (The New England Journal of Medicine), in a field with very limited available evidence. One could expect that these striking results would have at least

drawn the attention of the majority of PICU physicians. Despite the scarcity of (causal) evidence, 1 out of 3 respondents would wait for updated guidelines published by prominent scientific societies before deciding on their PN practices. A finding that stresses the importance of up-to-date guidelines. The time between the previous and current versions of international guidelines regarding nutrition for critically ill children is 8 to 13 years.[74,99,103,104] These updated European and American guidelines have based their recommendation regarding the timing of initiating PN on the PEPaNIC results. However, their interpretation and recommendations differ. The European guideline states that withholding PN for 1 week can be considered,[99] while the American guideline recommends to withhold PN for 1 week only for patients with normal baseline nutrition state and low risk of nutrition deterioration.[74] Based on expert opinion, the American guideline suggests to start PN earlier in children without any EN and those who are undernourished on admission to the PICU.[74] The recent results of Late-PN versus Early-PN in critically ill, undernourished children **(Chapter 4)** were published after the development of the current American guideline.

Other frequently reported barriers for de-implementing Early-PN were the conviction that children need amino acids, concerns that withholding PN could be harmful in neonates and undernourished children, and that respondents were waiting for long-term results and replicating studies **(Chapter 2)**. We have addressed most of these issues in the past 2 years **(Chapter 3, 4 and 6),** which might enhance de-implementation of Early-PN worldwide in the forthcoming years.

Key messages

- Withholding PN during the first week of critical illness in children was previously found to be clinically superior to early initiation of PN.
- Despite these results, initiation of supplemental PN within the first week is still considered essential in three-quarters of PICUs worldwide.
- The following factors hampered de-implementation of Early-PN: low awareness of new results, awaiting updated international guidelines, and specific concerns for need for amino acids, safety in neonates and undernourished children, and long-term safety.

Are amino acids essential in the acute phase

Our survey pointed out that amino acids are the component of PN considered to be most essential **(Chapter 2)**. This belief in the beneficial effect of protein comes from systematic reviews, including small randomised studies, showing that higher protein intake results in a positive protein balance.[3,120] However, whether achieving a positive protein balance translates into prevention of muscle wasting or other clinical benefit has not been investigated. In preterm neonates, more research regarding amino acids has been done, although in this population the majority of RCTs also used surrogate outcome measures. One

randomised study showed that providing amino acids directly following birth resulted in better mental development in premature boys, but not in girls.[215] However, because of physiological and pathophysiological differences between preterm infants and term neonates or older children, these results cannot be extrapolated. In a subgroup of critically ill adults from the randomised EPaNIC trial, lower nutrient intake by delaying PN with 1 week (including the delay of parenteral amino acids) did not lead to more muscle wasting as compared with Early-PN, but actually resulted in a decreased incidence of muscle weakness.[55] Furthermore, a secondary analysis of the EPaNIC trial showed that it was not the cumulative dose of glucose or lipids, but of protein/amino acids that could explain the observed clinical harm caused by Early-PN.[128] These harmful effects of amino acids were confirmed in critically ill children from the PEPaNIC study.[70] Even in low doses of 20-30% of target, protein/amino acid administration was associated with slower recovery.[70] Maximum harm was found when amino acid intakes increased up to 1.15 g/kg/day in children weighing up to 10 kg, 0.83 g/kg/day in children weighing 10 to 20 kg, and 0.75 g/kg/day in children weighing more than 20 kg,[70] which are much lower thresholds than currently recommended.[74]

A possible explanation might be related to autophagy, an efficient housekeeping mechanism involving the lysosomal degradation of cytoplasmic organelles or cytosolic components.[216] Degraded contents are eliminated or recycled to maintain nutrient and energy homeostasis.[216] Autophagy is activated by cellular stress, and plays an important adaptive role in cellular damage control and preservation of endogenous energy supply during critical illness.[132,133] Importantly, this process is inhibited by nutrients.[132] In rabbits, administration of PN early during critical illness, in particular amino acids, resulted in decreased activation of autophagy in muscle and liver.[132] These animal models suggest that adequate activation of autophagy could be necessary to properly heal damaged cells or tissues, and that delaying PN might support autophagic activity, and thus inhibit subsequent ongoing cellular damage and prevent clinical complications. In fact, in critically ill adults, withholding PN for 1 week resulted in increased activation of autophagic quality control of myofibres and decreased muscle weakness as compared with initiating PN <48 hours.[55] If this can be extrapolated to critically ill children is currently unknown. Another explanation could be that the body copes differently with excessive amounts of different nutrients. Whereas excessive intakes of carbohydrates and lipids can be stored as fat, too much intake of amino acids has to be converted into urea by the liver to subsequently be excreted in urine, which imposes a burden to the kidneys. Indeed, in critically ill children, plasma urea concentrations during the first week were higher if PN was initiated early **(Chapter 3)**.[70] In the acute phase of illness, protein requirements might differ from those during health, which could lead to an excess of amino acids if the targets are not being reduced. It would be interesting to investigate whether no or very low protein intake (enterally and parenterally) in the acute phase of critical illness would be beneficial as compared with current recommended intake of protein[74] with a randomised design and clinically relevant outcome measures, such as incidence of new infections, duration of mechanical ventilation, length of stay, organ function, long-term physical and neurocognitive functioning, and quality of life.

Key messages

- The cumulative doses of protein/amino acids, but not glucose or lipids, could explain the harm caused by Early-PN.
- Autophagy plays an important role in controlling cellular damage, which is suppressed by nutrients, in particular amino acids.

Late PN in neonates and undernourished children

Within the heterogeneous group of critically ill children, there are some subgroups of children who are considered susceptible to be harmed by macronutrient restriction. Because of limited glycogen and fat stores, neonates and undernourished children are considered more prone to effects of low macronutrient intake. As such, concerns were raised on the efficacy and safety of withholding PN in these specific patient groups **(Chapter 2)**.[71-73,75,217]

Critically ill, term neonates

As nutrition and metabolism change remarkably during the first 4 weeks of life, even during normal physiology in a healthy neonate, we investigated the effect of Late-PN in critically ill, term neonates within different age groups: ≤4 weeks, ≤1 week and <1 day. In all age groups, Late-PN resulted in a higher likelihood of an earlier weaning from mechanical ventilation alive as compared with Early-PN. In neonates ≤4 weeks and ≤1 week, Late-PN led to a higher likelihood of an earlier discharge from PICU alive, and in neonates ≤1 week and <1 day to a lower risk of new infections **(Chapter 3)**. In all age groups, Late-PN did not affect survival up to day 90 **(Chapter 3)**. It should be noted that the group of neonates <1 day was small and that the diagnoses differed between the randomisation groups. The Early-PN group consisted of significantly more newborns with congenital diaphragmatic hernia than the Late-PN group, while the proportion of newborns with gastroschisis was lower. These baseline differences warrant caution when interpretating the results within this age group. Furthermore, we were unable to formally test an age-dependent effect, since the sample size would become too small if we would separate the groups. However, when comparing the hazard ratios (HR) of time to discharge alive in the children older than 4 weeks (HR 1.17, 95% CI, 1.04-1.31)[18] with those of neonates aged ≤4 weeks (HR 1.61, 95% CI 1.19-2.20) and ≤1 week (HR 1.69, 95% CI 1.16-2.46) **(Chapter 3)**, and the finding that the beneficial effect of Late-PN on long-term neurocognitive functioning was more pronounced in children who were infants on admission **(Chapter 6)**, withholding PN appears to be most beneficial in the youngest patients. An important safety outcome in all age groups was the increased risk of hypoglycaemia with Late-PN, although all episodes were brief and asymptomatic. This finding stresses the need for close monitoring of blood glucose levels when PN is withheld to detect and treat hypoglycaemia timely. Symptomatic, prolonged and recurrent hypoglycaemia is associated with negative consequences on long-term neurocognitive functioning.[135] However, recent well-designed

studies on the long-term consequences of brief episodes of asymptomatic hypoglycaemia in preterm neonates and healthy newborns have shown no clear harm.[19,21-23] Furthermore, critically ill infants and children examined 4 years after an RCT about glycaemic control did not show an association between hypoglycaemic incidents and neurocognitive functioning.[20] In our 2-year follow-up, the beneficial effects of Late-PN versus Early-PN on long-term outcomes also did not appear to be mediated by its acute effect on exposure to hypoglycaemia **(Chapter 6)**. Despite the fact that brief, asymptomatic hypoglycaemia does not seem to have long-term repercussions, the low amount of glucose administered to neonates in the Late-PN group is of notice. These neonates received approximately 1.4 mg/kg/min glucose **(Chapter 3)**, while the most recent European guideline advices to start with 2.5-5.0 mg/kg/min, and gradually increase to 5-10 mg/kg/min in 2-3 days from day 2 onwards in critically ill, term neonates.[218] In a secondary analysis of the PEPaNIC trial, it was found that higher doses of glucose in the first days after admission were associated with a lower the risk of new infections.[70] Hence, future studies could consider administering higher doses of glucose then currently done in the PEPaNIC trial. Furthermore, higher doses of lipids beyond the first few days could also be beneficial.[70] Although not significant, the same patterns were found in term neonates **(Chapter 3)**. Furthermore, in term neonates, higher doses of protein/amino acids were associated with harm **(Chapter 3)**, in line with previous findings in adults and children aged 0-17 years.[70,128] As Early-PN, containing amino acids, glucose, and lipids, was associated with harm, apparently, the higher amount of glucose and lipids could not offset this harm evoked by amino acids.

Key messages

- Late-PN was clinically superior to Early-PN in critically ill, term neonates. However, clinicians should monitor blood glucose levels closely when PN is withheld.
- The youngest patients appeared to benefit most from Late-PN.
- Protein/amino acid intake was associated with harm in critically ill, term neonates.

Critically ill, undernourished children

Another subgroup of vulnerable children is the group of children who are undernourished on admission to the PICU. Previous studies have shown an association between acute undernourishment and worse clinical outcomes.[33,35,36] This was confirmed in the PEPaNIC study, showing that acute undernourishment on admission, defined as a weight Z-score <-2, was associated with a prolonged duration of PICU stay and hospital stay, and a higher incidence of hypoglycaemia during the first week as compared with well-nourished children **(Chapter 4)**. However, the group of undernourished children differed from the well-nourished children with regard to several baseline characteristics, among others severity of illness and

primary diagnosis **(Chapter 4)**, which suggests that many other, not tested, variables differ between the groups, for example, type and doses of medication, and co-morbidities. We have corrected the analyses for a few of these baseline differences, however, obviously, it is impossible to correct for all potential differences. Hence, it is questionable if the observed worse clinical outcome can be attributed to the nutritional status itself or to other factors that may have played a role. Current American guidelines recommend that PN might be started earlier in children who are undernourished on admission than in well-nourished children.[74] The rationale behind this suggestion is that higher caloric intake by PN might prevent further weight deterioration and subsequently improve clinical outcomes of undernourished children. However, it was unknown whether prevention of weight deterioration and improved outcomes in undernourished children can be achieved by early supplementation of PN. The PEPaNIC trial, with its randomised design and a large group of undernourished children, provided an opportunity to investigate this hypothesis. As was found in the PEPaNIC population as a whole, also in critically ill undernourished children, Late-PN resulted in a lower risk of new infections and faster recovery facilitating earlier weaning from mechanical ventilation alive and earlier PICU discharge alive **(Chapter 4)**. Furthermore, Late-PN did not affect mortality, the risk of hypoglycaemia, and incidence of weight Z-score deterioration during PICU stay **(Chapter 4)**. In severely undernourished children, Late-PN was also beneficial as compared with Early-PN. Possible explanations for these results in undernourished children remain speculative. First, as mentioned above, acute undernourishment on admission could be an expression of severe illness. Both in adults and children, the severity of illness and concomitant inflammation is considered to play a role in the development of undernutrition, although the precise mechanisms are largely unclear.[158,159] This might explain the worse clinical outcome associated with undernourishment on admission. Second, it is suspected that undernourished children have an altered immune response as compared with well-nourished critically ill children, among others in cells that are involved in fasting-induced autophagy,[149,219] which might have hindered efficient autophagy. Therefore, undernourished children could hypothetically be even more susceptible to the detrimental effects of Early-PN. More research is needed to unravel the underlying mechanisms of the interplay between nutritional status and immunological alterations for a better understanding how to treat these children. Furthermore, the optimal timing of initiating PN in undernourished critically ill children might differ from well-nourished children. However, currently, it is unknown whether PN should be initiated earlier in undernourished children to prevent further deterioration of their nutritional status, or later to support their immune system and autophagic activity longer.

Key messages

- Undernourishment on admission was associated with worse clinical outcome, although many baseline characteristics differed between undernourished and well-nourished children. Therefore, we cannot preclude that other factors might also have played a role.
- Undernourished children, defined as weight Z-score <-2, benefitted from withholding PN during the first week in PICU.

Changes in nutritional status during PICU stay

In previous observational studies, it was found that children admitted to the PICU on average show a decline in several Z-scores of nutritional status parameters at different endpoints.[4-7,42,156] Improvement of a nutritional status has been associated with higher nutritional intake, although only in observational studies, which requires caution when interpreting these results.[5-7,42] We investigated whether there is a relationship between withholding PN during the first week in PICU and change in nutritional status, and found that this did not affect the change in weight Z-score during PICU stay as compared with Early-PN **(Chapter 5)**. Additionally, withholding PN did not affect the average change in weight Z-score per day **(Chapter 5)**.

Possible explanations remain speculative. In a systematic review, nutritional intake above 57 kCal/kg/day was found to result in a positive nitrogen balance in critically ill children.[3] However, none of the included studies investigated whether this translates into improved nutritional status. The acute phase of critical illness is characterised by whole body protein breakdown and muscle loss. In critically ill children, it was shown that muscle mass, measured with ultrasound as thickness of the femoral quadriceps, decreased up to 13% during PICU stay.[49] This muscle wasting often persists because of disease related factors, but also iatrogenic factors, such as medication and immobilisation. In critically ill adults, supplemental PN during the first week did not affect muscle wasting.[55,57] Hence, there seems to be no benefit of supplemental PN in the acute phase of illness to prevent muscle wasting. However, supplemental PN in the stable and recovery phase might play a role in preventing further deterioration.

On admission to the PICU, the median weight Z-score was -0.72 **(Chapter 5)**. A previous observational study in critically ill term neonates and older children found catch-up growth 6 months after PICU admission.[42] In line with this finding, anthropometric measurements of PICU-survivors 2 years after enrolment in the PEPaNIC study revealed Z-scores of height -0.07, weight -0.15, BMI -0.25 and head circumference -0.11, although these Z-scores were still significantly lower than those of matched healthy children **(Chapter 6)**. Importantly, there were no differences in Z-scores between the Early-PN and Late-PN groups **(Chapter 6)**. Also, the change in Z-scores between PICU admission and 2-years follow-up was similar in both treatment groups **(Chapter 6)**. Altogether, although the nutritional intake was significantly

lower during the first week, Late-PN did not have consequences on the nutritional status during PICU stay and of PICU survivors 2 years after admission. Of notice, we did not correct the weight Z-scores for ethnicity or presence of a syndrome, which could have influenced the weight Z-scores. However, as there were no differences in ethnicity nor in proportions of patients with a (suspected) syndrome between the Late-PN and Early-PN groups, this does not compromise our comparisons of Late-PN versus Early-PN. Future studies could consider an additional assessment of body composition by use of BIA or air-plethysmography months to years after PICU admission, as this can give more information on the effects of nutritional strategies on the evolution of body composition than anthropometric measurements. Age-dependent reference values of BIA[220] and air-plethysmography[221-223] are available for all paediatric age groups, although there is a need for updated, accurate reference values.[224]

Weight Z-score deterioration was associated with a lower likelihood of an earlier discharge from PICU alive and with a higher risk of new infections **(Chapter 5)**. However, since the change in weight Z-score was not significantly different between the treatment groups, deterioration of weight Z-score does not seem to be a consequence of PN intake during the acute phase but may reflect severe illness. In a guideline on defining paediatric malnutrition, the severity of inflammation is recognised to influence the occurrence or deterioration of disease-related malnutrition, although its exact role is not yet understood.[158] In adults, malnutrition is also considered to be related to disease burden/inflammation.[159] Given that withholding PN did not affect the change in weight Z-score, but still resulted in enhanced recovery, the value of the change in weight Z-score during the acute phase of critical illness is questionable. A few other measurements could be considered that could reflect the nutritional status better. Mid-upper arm circumference is less influenced by oedema, easy to obtain in critically ill children and can be used to estimate a child's weight.[32,164] Another measure of undernourishment is the phase angle by use of bio-electrical impedance analysis (BIA). The phase angle on admission and on the second day has recently been shown to be related to the duration of PICU stay.[46] Whether the evolution of the phase angle during critical illness may guide nutritional interventions is currently unknown. Another important measurement might be the loss of muscle mass or decrease in muscle quality. Interestingly, in critically ill adults, CT images showed that withholding PN during the first week improved the muscle quality reflected by decreased amounts of adipose tissue within the muscle compartments, as compared with PN initiation within 48 hours.[57] Muscle mass decreased during the first week, but this decrease was unaffected by PN.[57] Moreover, muscle weakness was reduced in patients receiving Late-PN.[55] It is unknown whether these results can be extrapolated to children. Little is known about critical illness related polyneuropathy in children as well. Muscle biopsies for scientific purposes in children are considered too invasive, and the evidence for reliability of ultrasonography to detect muscle wasting is inconsistent.[49,165] However, handgrip strength tests in the long term might be feasible and could add value to exploring the long-term effects of nutritional interventions.[225] This test can be done in children from the age of 4 years and age- and sex dependent reference values are available.[225,226]

Key messages

- Less weight Z-score deterioration was associated with worse clinical outcomes.
- Late-PN did not affect change in weight Z-score during PICU stay.
- The value of change in weight Z-score to evaluate nutritional interventions in the acute phase of critical illness is questionable.

Long-term efficacy and safety of Late-PN

Two years after participation in the PEPaNIC study, PICU survivors had worse developmental outcomes as compared with healthy matched control children in numerous domains reflecting growth, health status, intelligence, executive functioning and behaviour **(Chapter 6)**. These observed deficits confirmed previous findings in follow-up studies of critically ill children.[20,80-82,87,89-95] Late-PN did not negatively affect survival, anthropometrics, health status, and neurocognitive development. Moreover, of the patients who survived, fewer were too disabled to be tested in the Late-PN group than in the Early-PN group **(Chapter 6)**. Interestingly, Late-PN improved parent/caregiver-reported executive functioning, inhibition in particular, as compared with Early-PN **(Chapter 6)**. In fact, children in the Late-PN group did not perform worse on inhibition tests than healthy children **(Chapter 6)**. Executive functioning, which is the ability of complex decision making and goal-oriented behaviour, is important in many aspects of daily life.[183] Thus, these long-term outcomes are relevant outcome measures with implications for daily life.

Explanations for the beneficial effects of withholding PN in the long-term are speculative. Epigenetic alterations, which denote cellular changes that affect gene activity and expression, might play a role,[188] since some of these changes have been associated with executive dysfunction.[183] Furthermore, telomeres, which are located at the ends of the chromosomes to protect chromosomes from degradation, might be involved. Telomeres shorten with each cell cycle, but also under influence of oxidative stress and inflammation.[227,228] Recently, telomeres of critically ill children were found to be shorter on admission to the PICU than those of healthy children, and further shortening during PICU stay was accelerated by Early-PN,[126] which might have long-term consequences. Unraveling the underlying mechanisms could contribute to a better understanding of the complex situation of paediatric critical illness and the role of nutrition during this period, and might provide new insights into possible treatment options for critically ill children.

A limitation of this study is the young age of the patients at follow-up with a median age of 5.7 years. The included neonates and infants, comprising half of the original study population, were followed-up at age 2.5 years old, as this was the lower boundary of the test for Intelligence Quotient (IQ). Because of their age at follow-up, the youngest children could not complete all tests. The most pronounced benefit of Late-PN was found in inhibition as reported by the parent or caregiver, but the clinical test to actually measure inhibition was not suitable for children younger than 4 years. Furthermore, some other significantly different

domains, such as motor coordination and memory, could not be tested in the youngest children as well. Since children who were infants at randomisation benefitted more from Late-PN than older children on several parent/caregiver-reported executive functions, it could be expected that the beneficial, clinically tested effects of Late-PN in the whole group might have been larger if also the youngest children could have completed all tests.

In this study, the Wechsler Intelligent Scales were chosen to measure Intelligent Quotients (IQ), which can be used from the age of 2.5 years onwards into adulthood. Given that a certain degree of neurodevelopmental delay was to be expected in post-PICU patients, it is questionable if the Wechsler Intelligent Scale is the optimal test for the youngest children age 2.5 years old. Perhaps, a developmental test, such as the Bayley Scales of Development,[229,230] might have provided more information on neurodevelopment of the youngest children. However, an important argument to use the Wechsler Intelligent Scales in this setting is that it comprises comparable results on IQ along a broad age-range, which facilitates comparisons between age groups and, more importantly, over time. Since an even longer follow-up of our patients is currently ongoing, the longitudinal value was an important aspect to take into account.

A few studies have looked into the IQ of children after critical illness and found a lower IQ compared to healthy children.[20,91,93] Other studies in children with oesophageal atresia,[231] congenital diaphragmatic hernia,[232] and after neonatal extracorporeal membrane oxygenation[90] found an IQ within the normal range. Interestingly, all of these studies found that patients had a worse development of other cognitive functions, such as memory, attention, and executive functioning. Moreover, following the 'growing into deficit' principal, it can be expected that neurocognitive deficits, in particular in executive functioning, will be more pronounced when children grow older and demands for their neurocognitive abilities increase. A previous longitudinal study at 2, 5 and 8 years after neonatal extracorporeal membrane oxygenation found that the average IQ was within the normal range and remained stable over time.[91] However, despite a normal IQ, a large group needed extra help in school, which was associated with lower attention, one of the executive functions.[91] This is in line with the findings in our study **(Chapter 6)** and stresses the importance of long-term follow-up of PICU-survivors with an extensive neurocognitive evaluation comprising more than merely testing of IQ.

The effect of Late-PN on executive functioning might point towards a protective effect on the cerebral frontal lobe.[185] Since maturation of the prefrontal cortex continues into late adolescence, executive functioning is among the last brain functions that a child develops.[233] Therefore, mildly impaired executive functioning might not yet be apparent in young children. Moreover, this late maturation makes the prefrontal cortex particularly susceptible to disruption. Consequently, a child who has acquired brain damage early in life could be confronted with problems related to executive functions getting more pronounced with increasing age, such as planning and decision making. Preventing or decreasing brain damage due to critical illness early in life might reduce the long-term burden for these children. Since Late-PN already showed to have a beneficial effect on parent/caregiver-reported executive

functioning 2 years after critical illness, this effect might be amplified later in life. Thus, since the children are older at longer follow-up, and therefore able to complete all tests, and because of the possibility of growing into deficit, a longer follow-up of the children would give more insights into the long-term 'legacy' of critical illness and the effect of Late-PN hereon.

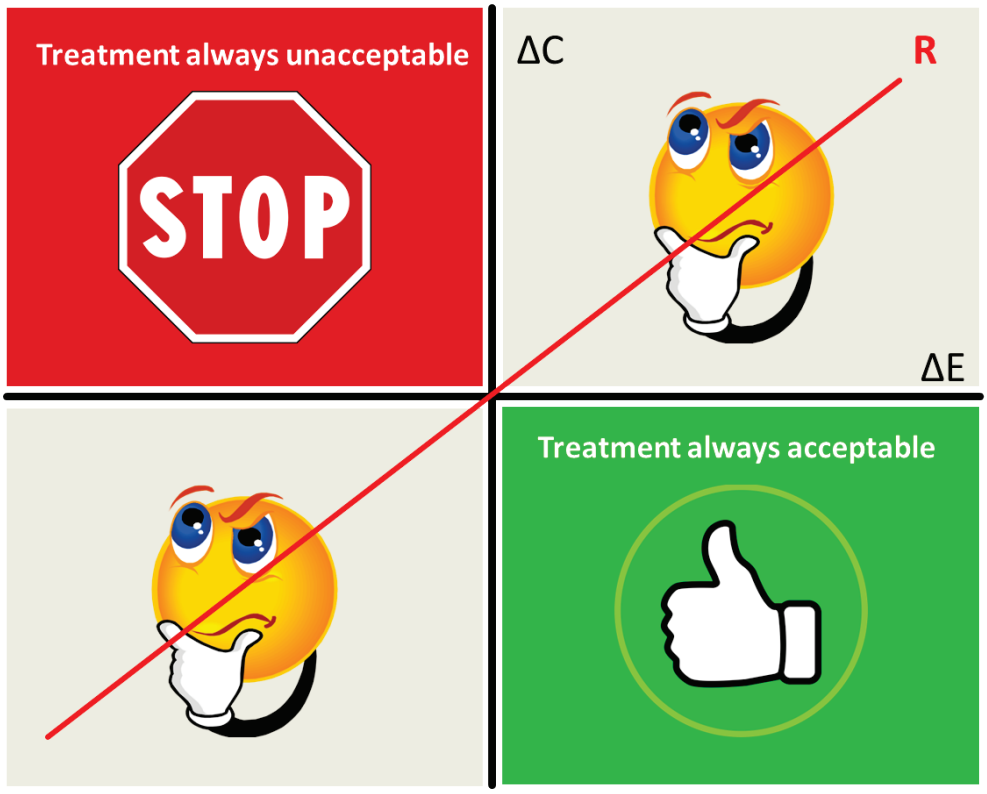
Key messages

- Post-PICU patients had a normal IQ, but performed worse on many neurocognitive domains compared to healthy, matched peers, which stresses the need for long-term follow-up after critical illness.
- Late-PN resulted in better inhibitory control, as reported by parents/caregivers, compared to Early-PN.
- Since the youngest children were too young to complete all tests, the neuropsychological effects of Late-PN should be re-evaluated when the children are older.

Cost-effectiveness of Late-PN

Treating a severely ill child in the PICU has consequences not only for a child and a family but also imposes a burden on society. The intensive treatments, diagnostics, and care for these patients are costly. Moreover, indirect costs, such as parental absence from work, have financial consequences as well. With increasing healthcare expenses during the past years,[234] the cost-effectiveness of an intervention is of increasing interest. We calculated direct medical costs during hospital stay from a hospital perspective with a micro-costing approach and compared the Late-PN group with the Early-PN group. We found that Late-PN is a cost-saving strategy, which saves on average 7180 euro per patient, reflecting 21% of the total direct medical costs per patient **(Chapter 7)**. Cost-effectiveness of a treatment can be divided into 4 quadrants (Figure 1). If the costs of an intervention are higher but less effective (north-western quadrant), the treatment is always unacceptable. On contrary, if an intervention is both effective and cost-saving (south-eastern quadrant), the treatment is always acceptable. In case of a more expensive, but also more effective treatment, or cost-saving at the expense of reduced efficacy, the decision to accept a treatment depends on the incremental cost-effectiveness ratio (ICER) and the willingness to pay. Thus, it depends on how much money the society is willing to pay for 1 unit of health benefit, which is generally expressed as quality-adjusted life year (QALY) gained.[200]

Figure 1. Cost-effectiveness plane



ΔC = difference in costs between intervention and control; ΔE = difference in effects between intervention and control; R = boundary of willingness to pay.

Thus, in the case of Late-PN, given the clinical benefits and lower costs of Late-PN, this intervention falls into the south-eastern quadrant of a cost-effectiveness plane and was thus highly cost-effective. Further assessments of cost-effectiveness, such as calculating the ICER, were redundant. The top three cost categories that contributed to the difference in costs were PICU hospitalisation (which included costs for personnel, electricity, et cetera), medication and ventilator support, which together comprised 75% of the cost reduction by Late-PN, although almost all cost categories were reduced by Late PN **(Chapter 7)**. The cost reduction of PN itself contributed only 2.1% to the total cost reduction, which confirmed our hypothesis that the health-economic impact of withholding PN encompassed more than omission of the costs for PN itself **(Chapter 7)**. The occurrence of new infections appeared to be an important factor contributing to the costs, as the proportion of patients who acquired a new infection was highest in the most expensive patients, even up to 85% in the 1% most expensive patients **(Chapter 7)**. This is in line with a previous observational study, which reported higher costs in children with a new infection as compared with children without a new infection.[96] Hence,

reducing the duration of PICU stay by preventing the occurrence of new infections by Late PN seems to have had most influence on the cost reduction **(Chapter 7)**.

The effect measure of this cost-effectiveness analysis was *a priori* defined as the number of prevented infections. Although in cost-effectiveness analysis all types of relevant clinical outcomes are allowed to be used, using QALYs as effect measurement is generally preferable. However, the clinical value of QALY as short-term outcome measure in this specific study is questionable. Moreover, there are some ethical and practical obstacles to assess the quality of life in children shortly after they have been admitted due to critical illness. The cost-effectiveness of treating critically ill children has been investigated in neonates who required surgery for congenital diaphragmatic hernia or congenital anorectal malformations.[235,236] These studies showed that the health-related quality of life during the first 4 years of life was lower than that of healthy children. However, in adolescence, the patients had a health-related quality of life comparable with healthy peers. The costs of treating these children were approximately 2500 euro per QALY, which can be considered cost-effective.[235,236] Investigating the health-related quality of life of the PEPaNIC participants in the long term would be interesting, including assessment of the cost-effectiveness of Late-PN versus Early-PN.

Key messages

- Late-PN was cost-effective in the short-term and saved approximately 7000 euro per patient.
- Preventing new infections was an important factor to reduce direct medical costs.

CLINICAL IMPLICATIONS

The studies described and discussed in this thesis have confirmed the beneficial clinical effects of withholding PN during the first week in critically ill term neonates and undernourished children, in the long term and have shown the short-term, health-economic benefits **(Chapter 3, 4, 6 and 7)**. Late-PN versus Early-PN was investigated while providing intravenous trace elements, vitamins, and minerals to children in both groups. As these micronutrients are usually dissolved in PN, it is required to provide them separately to prevent complications due to deficiencies. Furthermore, the occurrence of hypoglycaemia should be monitored closely to treat this appropriately and quickly. If a PICU can fulfill these requirements, based on the currently available evidence, it can be recommended to withhold PN during the first week of paediatric critical illness.

The increased risk of hypoglycaemia with Late-PN was most pronounced in term neonates. Taking the risk of hypoglycaemia and the macronutrient results into account **(Chapter 3)**, in term neonates it could be considered to provide a higher glucose intake than now provided in the Late-PN group, without administering amino acids during the first week of critical illness.

In undernourished children, as well as well-nourished children, the optimal timing of initiating PN is currently unknown. As undernourishment on admission has consistently been associated with worse clinical outcomes **(Chapter 4)**, physicians tend to start PN earlier in undernourished children than in well-nourished children **(Chapter 2)**. However, up to date, there is no evidence showing that PN in the acute phase is capable of preventing undernourishment or deterioration of the nutritional status **(Chapter 5)**. On the other hand, our study showed that also the children who were undernourished on admission benefitted from withholding PN during the first week of critical illness **(Chapter 4)**. Therefore, withholding PN for a week in undernourished children seems to be the best approach with current knowledge.

The results from our 2-years follow-up recognise the long-term consequences of paediatric critical illness that our patients can be confronted with **(Chapter 6)**. As a large proportion of children was younger than 4 years old at follow-up, their neurocognitive function could not be assessed completely. Despite these limitations, the extensive neurocognitive deficits that we identified when comparing the post-PICU patients with matched healthy control children underline the need for clinical follow-up of these children after discharge. This follow-up should not only consist of a medical evaluation of growth and physical function, but should also address neurocognitive function, including screening for executive dysfunctions, emotional and behavioural problems, and memory difficulties. Furthermore, our study showed that including parent/caregiver-reported outcome measures provide added value for evaluating neuropsychological functions **(Chapter 6)**.

RECOMMENDATIONS

Based on the results presented in this thesis and the available evidence with clinically relevant outcomes as discussed, we conclude and recommend the following:
withholding PN during the first week of critical illness in children, while administering micronutrients, …

1. can be considered, as this resulted in short-term and long-term benefits, with concomitant reduction of healthcare costs.
2. is clinically beneficial in term neonates. Since the risk of hypoglycaemia is increased when PN is withheld, close monitoring of glucose levels is required to detect and treat hypoglycaemia adequately.
3. is clinically beneficial in undernourished children, defined as weight Z-score <-2.

Other recommendations are:

4. Nutritional interventions during the acute phase of critical illness should aim at improving organ function and clinical outcomes.
5. It is recommended to investigate the effect of a nutritional intervention not only in the short term and but also in the long term since short-term surrogate outcomes can contradict with clinically relevant long-term outcomes.
6. Long-term follow-up should not only consist of a medical evaluation of growth and physical function, but should also address neurocognitive function, including the occurrence of executive dysfunction, emotional and behavioural problems, and memory difficulties.
7. Due to increasing healthcare expenses, cost-effectiveness assessment should be an integral part of (nutritional) interventional research to enhance sustainable healthcare.
8. Decreasing the duration of PICU stay by reducing new infections, is a major target to cut direct medical costs.

FUTURE PERSPECTIVES

The short-term and long-term results of the PEPaNIC study underline the clinical importance of nutritional management. The recently published intensive care medicine clinical research agenda in paediatrics highlights the importance of further exploring feeding strategies in the next 10 years.[237] The results described in this thesis have answered some important questions, but also raised new questions. Based on this thesis, future nutritional studies in PICU should focus on 3 areas:

- unraveling underlying mechanisms of macronutrient restriction during the acute phase;
- exploring the optimal timing and composition of (parenteral) nutrition;
- further evaluating long-term consequences of critical illness in children.

Unraveling underlying mechanisms

Mechanistic studies provide more insight into underlying mechanisms of withholding PN, which in turn might reveal new opportunities to further improve outcomes. Endocrine responses in relation to nutritional interventions will be explored. Furthermore, the relationship between nutritional intervention, shortening of telomeres and long-term outcomes will be analysed. Finally, the role of epigenetic alterations will be explored. Early initiation of PN could alter an epigenetic profile, which might be related to worse long-term outcomes. These pre-planned mechanistic studies are currently ongoing and eagerly awaited.

Exploring the optimal timing and composition of nutrition

As with all new insights, these findings need to be confirmed with other studies. Furthermore, the PEPaNIC study compared initiating PN at day 1 to withholding PN during the first week in PICU. Such a strict and large difference in timing of initiating PN is necessary for scientific research to set a framework. However, this might not represent the optimal timing. Inevitably, there is a crossover point at which macronutrient restriction is no longer needed and will not be beneficial anymore. This timing is likely different per person and might also differ between age groups or could be depending on nutritional status. Therefore, an individualised approach is preferred. However, until now there is no set of biomarkers sufficiently sensitive and specific to predict when a patient is ready to receive PN or full EN. When evaluating effectiveness of such an individualised approach, this should ideally be compared with current nutritional practices in a randomised study using clinical outcomes.

Assuming that a fasting response indeed is responsible for accelerated recovery from critical illness by withholding PN, then further amplification of this fasting response might result in even better clinical outcomes. Taking into account that amino acids/protein from EN and PN cumulative was associated with harm, a possible way to intensify the fasting response could be to reduce the amount of enteral protein during the acute phase while withholding PN. Investigating a strategy without providing any protein could be of interest.

Another way to support the fasting response in the acute phase could be intermittent enteral feeding and after the first week intermittent PN and/or EN. When investigating this

strategy, the time between the periods of nutrient delivery should be sufficiently long to facilitate complete macronutrient uptake from EN and to induce a fasting response. Ideally, this intermittent feeding strategy would take into account the age-dependent circadian rhythm.

Evaluating long-term consequences

With regard to long-term outcomes, many questions are yet to be answered. As the youngest children were too young to complete all assessments, some neurocognitive domains have to be evaluated in these children in future studies. When children grow older, the demands for their neurocognitive abilities increase. Subsequently, deficits will become more clear with increasing age and neurocognitive tests should therefore be repeated when the children are older.

Our long-term follow-up identified the duration of treatment with benzodiazepines and corticosteroids as independent risk factors for worse neurocognitive outcome. Future, randomised studies are needed to investigate the effects of these medications in critically ill children.

With all beneficial short-term and long-term effects of withholding PN as described in the literature and in this thesis, one could expect a positive effect on the quality of life of both the children and their parents as well. This will be a topic of research in the near future. Related to this topic is the assessment of QALYs, which can be used in long-term cost-effectiveness analysis. When an effect is expressed as number of QALYs gained, cost-effectiveness of different interventions can be compared with each other, which can be of added value in clinical decision making.

CONCLUSION

In critically ill children, irrespective of nutritional status or age, withholding PN during the first week, while administering micronutrients, was shown to be clinically beneficial in the short term and long term, as well as from a health economic point of view. By withholding PN in the acute phase of critical illness, the literal, as well as the figurative price to pay for paediatric critical illness can be reduced for children, their families, and society.

Chapter 9

Summary / Samenvatting

SUMMARY

Chapter 1

A significant proportion of critically ill children are unable to eat and drink themselves and therefore rely on artificial nutrition. Therefore, establishing optimal nutrition in sick children is generally accepted as essential therapy to enhance recovery from illness and to facilitate long-term growth and development. However, defining 'optimal nutrition' in paediatric critical illness is difficult because of heterogeneity in age, body composition, and the children's underlying diseases and co-morbidities. Optimal nutrition differs not only between individual patients but also within a patient over time, during the different phases of critical illness: acute, stable, and recovery.

Another problem with defining 'optimal nutrition' is the lack of support by high-level evidence to support timing, amount, and route of artificial nutrition in critically ill children. In the first chapter, we showed that most studies on nutrition for children admitted to the paediatric intensive care unit (PICU) used surrogate outcomes. We tried to provide insight on the imbalance between nutritional studies in critically children with surrogate and clinical outcome measures with help of a 5-step model consisting of surrogate outcome measures (step 1 biochemical indices, step 2 body composition, and step 3 organ function) and clinical outcome measures (step 4 short term outcome and step 5 long term and health-economic outcome). We summarized the current literature within each of these steps. The review in chapter 1 stresses the lack of well-designed, randomized trials with clinical endpoints that reliably validate current recommendations. This thesis focused on steps 4 and 5 to explore optimal nutrition in critically ill children.

This thesis further elaborates on the results generated by the Early versus Late Parenteral Nutrition in the Paediatric Intensive Care Unit (PEPaNIC) randomized controlled trial, published in The New England Journal of Medicine in 2016, which showed that withholding parenteral nutrition (PN) during the first week (Late-PN) was clinically superior to initiation of PN at day 1 (Early-PN). Chapter 1 finishes with the aims and hypothesis of this thesis.

Chapter 2

Results from a worldwide survey showed that 1 year after the results of the PEPaNIC study were published, the majority of PICUs still administer PN during the first week of critical illness. However, about a quarter of the respondents opted to postpone PN beyond the first week, of whom half already withheld PN and half had de-implemented Early-PN. The most important reasons for retaining early initiation of PN were the conviction that amino acids are essential for critically ill children, doubts on the efficacy and safety of withholding PN for a week in undernourished children and neonates, and concerns on the long-term outcomes of delaying PN until after the first week. These findings supported that the objectives addressed in this thesis are meaningful in clinical decision making, the development of new guidelines, and health-economic decisions.

Chapter 3

The neonatal population are a subgroup of critically ill children considered to be vulnerable to low nutritional intake. As many changes occur during the first month of life, we assessed the efficacy and safety of Late-PN in different age groups within the neonatal population included in PEPaNIC. In the subgroup of 290 term neonates ≤4 weeks, Late-PN was effective, except for the risk of new infections, which was not significantly different. However, Late-PN also resulted in a higher risk of hypoglycaemia. In neonates aged ≤1 week and neonates < 1 day, Late-PN was also effective, at the expense of a higher risk of hypoglycaemia. Interestingly, the effect seemed to have increasing impact for the younger children, suggesting an age-dependent effect. Further analyses revealed that in critically ill term neonates, higher cumulative protein/amino acid intake was associated with a lower likelihood of an earlier discharge from PICU alive and a lower likelihood of an earlier weaning from mechanical ventilatory support alive, whereas lipids beyond the first few days were associated with a higher likelihood of an earlier discharge from PICU alive and an earlier weaning from mechanical ventilator support alive while the relation for carbohydrate intake was neutral. We concluded that in critically ill neonates, Late-PN was effective and the harm caused by Early-PN could possibly be attributed to higher protein/amino acid intake rather than lipids or carbohydrates.

Chapter 4

In chapter 4, we assessed the efficacy and safety of withholding PN during the first week in undernourished children, another important population considered to be vulnerable to macronutrient deficits. This pre-planned subgroup analysis of the PEPaNIC trial showed that in children already undernourished on admission (n=289), withholding PN during the first week was clinically superior as compared with initiating PN on the first day, in line with results of the main cohort. While Late-PN reduced the risk of new infections and increased the likelihood of an earlier discharge from both the PICU and hospital alive, and also the likelihood of an earlier weaning from mechanical ventilatory support alive, the safety outcomes were not significantly affected. Furthermore, the group receiving Late-PN did not suffer from more weight deterioration than the group with Early-PN, although this could only be investigated in a subset of patients (n=100). In a subgroup of severely undernourished children, the results were in line with those of undernourished children. In summary, there was no support for early initiation of PN even in undernourished children; in fact, delaying initiation of parenteral nutrition appeared to be beneficial.

Chapter 5

Another major concern raised by nutritional experts after the publication of the PEPaNIC results was the effect on weight deterioration due to reduced nutritional intake. Therefore, for chapter 5, we selected a subgroup of children included in PEPaNIC with longitudinal weight measurements available on admission and at discharge from the PICU (n=470) to evaluate their course of weight. Less weight Z-score deterioration during PICU stay was associated with

a lower risk of new infections and with a higher likelihood of earlier PICU discharge from PICU alive. Late-PN did not affect change in weight Z-score during PICU-stay. Thus, there appears to be no role for Early-PN to prevent weight Z-score deterioration during the acute phase of critical illness. In regard to the weight Z-score change on the short term, Late-PN can be considered a safe approach.

Chapter 6

As we showed in chapter 1, clinical outcomes should be primary outcome parameters in the evaluation of nutritional therapies. Since survival rates have increased to >95%, the long-term outcomes of PICU survivors have become important. Several studies in various PICU populations have found that PICU survivors often suffer from a long-term 'legacy' of critical illness, both in physical and neurocognitive functioning. From previous follow-up research in children randomized to tight glycaemic control or standard care, we have learned that a metabolic intervention during paediatric critical illness is able to improve long-term neurocognitive development. Therefore, we followed-up the PICU survivors, assessing physical and neurocognitive functioning 2 years after participation in PEPaNIC, with a parallel group of healthy matched controls. With the results of PEPaNIC and those described in chapters 3 and 4 – a favorable short-term outcome with Late-PN, but higher risk of hypoglycaemia – in mind, these results were eagerly awaited.

PICU survivors performed worse in a number of domains as compared with healthy matched controls. Furthermore, Late-PN did not negatively affect survival, growth, physical health status nor neurocognitive development, and even improved inhibitory control compared to Early-PN. There was no observed difference in the effect of Late PN for children who experienced a hypoglycaemic incident during the first week in PICU, compared to children who did not.

Chapter 7

Alongside the short- and long-term clinical consequences of withholding PN, there is also an economic aspect. With increasing healthcare expenses, there is a need for sustainable, affordable healthcare decisions. To make these decisions, the costs of an intervention have to be traded-off against the health benefits. We have conducted a health-economic analysis, using a micro-costing approach to calculate the direct healthcare costs of Early-PN versus Late-PN, which showed that Late-PN saved, on average, approximately 7000 euro per patient. In considering the cost-saving elements versus the 7.3% reduction of new infections by Late-PN, it was undoubtedly found to be cost-effective, while further analyses, such as calculating an incremental cost-effectiveness ratio, were redundant. Children admitted for a medical reason other than neurologic disease represented the largest cost reduction, followed by children admitted for non-cardiac surgery. We found that the largest reduction in costs was achieved in PICU hospitalization costs, medication costs, and costs for ventilator support, which together comprised 75% of the cost reduction. Regarding medication costs, 80% of this cost reduction could be attributed to medications for "blood and blood-forming organs" and anti-

infective agents. When further looking into the role of new infections, we found that preventing new infections was an important factor that contributed to reducing costs. The difference in costs between children with and without a new infection was on average approximately 70.000 euro per patient in the Early-PN group and on average approximately 58.000 euro per patient in the Late-PN group, which was statistically significant. Thus, reducing the incidence of new infections by withholding PN seemed to be the key to reduce total direct healthcare costs.

Chapter 8

This chapter provides a reflection on the main findings described in this thesis. Implications of our research for clinical practice are outlined. We conclude that withholding PN during the first week of paediatric critical illness can be considered, as this was beneficial in the short-term – also in neonates and undernourished children –, in the long-term, and from a health-economic point of view. Based on our findings and currently available literature, recommendations for future nutritional research are made to further improve short-term and long-term outcomes of critically ill children. We propose that future nutritional research focuses on the following areas:

- unravelling the underlying mechanisms of macronutrient restriction during the acute phase;
- exploring the optimal timing and composition of (parenteral) nutrition;
- further evaluating long-term consequences of critical illness in children.

SAMENVATTING

Hoofdstuk 1

Een aanzienlijk deel van de kinderen die kritiek ziek zijn kunnen niet zelf eten en drinken. Daarom krijgen zij kunstmatige voeding. Optimale voeding voor zieke kinderen wordt gezien als essentieel voor het herstel van ziekte en om (lange termijn) groei en ontwikkeling te bewerkstelligen. Echter, de definitie van 'optimale voeding' in kritiek zieke kinderen is lastig vanwege de grote verscheidenheid in leeftijden, lichaamssamenstellingen en onderliggende ziekten van de kinderen. Optimale voeding verschilt niet alleen tussen individuele patiënten, maar ook per persoon in de tijd tijdens de verschillende fasen van kritieke ziekte: acuut, stabiel en herstel. Een ander probleem bij het definiëren van optimale voeding is het gebrek aan wetenschappelijk bewijs met hoge kwaliteit om de beste timing, hoeveelheid en route van kunstmatige voeding in kritiek zieke kinderen te ondersteunen. In het eerste hoofdstuk van dit proefschrift hebben wij laten zien dat de meeste onderzoeken over voeding voor kinderen die opgenomen zijn op de kinder-intensive-care afdeling (PICU) gebruik hebben gemaakt van surrogaat uitkomstmaten. We hebben gepoogd om inzicht te geven in de disbalans tussen voedingsonderzoeken met surrogaat en klinische uitkomstmaten met behulp van een 5-staps model bestaande uit surrogaat uitkomstmaten (stap 1 biochemische parameters, stap 2 lichaamssamenstelling en stap 3 orgaanfunctie) en klinische uitkomstmaten (stap 4 korte termijn uitkomsten en stap 5 lange termijn en gezondheids-economische uitkomsten). We hebben de bestaande literatuur binnen elk van deze stappen samengevat. Het overzicht in hoofdstuk 1 benadrukt het gebrek aan gerandomiseerde onderzoeken met klinische uitkomstmaten, waarmee de huidige aanbevelingen kunnen worden ondersteund. Dit proefschrift focust zich op stappen 4 en 5.

Dit proefschrift bouwt verder op de resultaten van het gerandomiseerde, gecontroleerde onderzoek over "vroeg versus laat starten van infuusvoeding bij kritiek zieke kinderen" (PEPaNIC) , wat in 2016 gepubliceerd is in The New England Journal of Medicine, waarbij gevonden werd dat het niet geven van infuusvoeding (parenterale voeding) gedurende de eerste week van opname op de PICU klinisch superieur was ten opzichte van het vroeg starten van parenterale voeding op dag 1. Hoofdstuk 1 eindigt met de doelen en hypothesen van dit proefschrift.

Hoofdstuk 2

De resultaten van onze wereldwijde vragenlijst lieten zien dat, 1 jaar na bekendmaking van de resultaten van het PEPaNIC onderzoek, op de meerderheid van de PICU's nog steeds parenterale voeding in de eerste week van kritieke ziekte gegeven wordt. Ongeveer een kwart van de respondenten vulden in dat ze parenterale voeding uitstellen tot na de eerste week, waarvan de helft dit al deed en de andere helft het vroeg starten met parenterale voeding gestopt (gede-ïmplementeerd) heeft. De belangrijkste redenen die gegeven werden om vroeg te blijven starten met parenterale voeding waren de overtuiging dat eiwitten essentieel zijn voor kritiek zieke kinderen, twijfels over de effectiviteit en veiligheid van het onthouden van

parenterale voeding in ondervoede kinderen en neonaten (kinderen jonger dan 1 maand) en zorgen over de lange termijn uitkomsten na het onthouden van parenterale voeding in de eerste week. Deze resultaten ondersteunden dat de onderwerpen die in dit proefschrift besproken worden belangrijk zijn voor nemen van beslissingen in de klinische praktijk, voor de ontwikkeling van nieuwe richtlijnen en bij het nemen van gezondheids-economische beslissingen.

Hoofdstuk 3

Een van de subgroepen van kritiek zieke kinderen die geacht worden extra kwetsbaar te zijn voor weinig voedingsinname is de groep neonaten. Omdat er gedurende de eerste levensmaand veel lichamelijke veranderingen optreden, hebben we de effectiviteit en veiligheid van het onthouden van parenterale voeding gedurende de eerste week in verschillende leeftijdsgroepen van a term geboren neonaten in het PEPaNIC onderzoek bekeken. In de subgroep van 209 neonaten ≤4 weken oud was het onthouden van parenterale voeding effectief, behalve voor het risico op nieuwe infecties, waarop geen significant effect werd gezien. Echter, het onthouden van parenterale voeding resulteerde ook in een hoger risico op lage bloedsuikers. Ook in neonaten ≤1 week en <1 dag oud was het niet geven van parenterale voeding effectief ten koste van een hoger risico op lage bloedsuikers. Het effect leek groter te worden naarmate de leeftijd jonger was, wat mogelijk wijst op een leeftijdsafhankelijk effect. Verdere analyses lieten zien dat in kritiek zieke a term geboren neonaten, hogere inname van eiwitten/aminozuren waren geassocieerd met een lagere waarschijnlijkheid om levend van de PICU ontslagen te worden en een lagere waarschijnlijkheid om levend van de ademhalingsondersteuning af te komen. Inname van vetten na de eerste paar dagen waren geassocieerd met een hogere waarschijnlijkheid om levend van de PICU ontslagen te worden en om levend van de ademhalingsondersteuning af te komen, terwijl de relatie tussen koolhydraten en klinische uitkomst neutraal was. Wij concludeerden dat in kritiek zieke neonaten het niet geven van parenterale voeding effectief was en dat de schade die veroorzaakt werd door het wel geven van parenterale voeding mogelijk toegeschreven kon worden aan de inname van eiwitten/aminozuren, en niet vetten en koolhydraten.

Hoofdstuk 4

In hoofdstuk 4 hebben we de effectiviteit en veiligheid van het onthouden van parenterale voeding gedurende de eerste week van kritieke ziekte in ondervoede kinderen beschreven. Kinderen die ondervoed zijn bij opname is een belangrijke groep die geacht wordt extra kwetsbaar te zijn voor weinig voedingsinname. Deze geplande subgroep-analyse van het PEPaNIC onderzoek liet zien dat kinderen die bij opname ondervoed zijn (n=289) voordeel hebben van het niet geven van parenterale voeding in de eerste week als dit vergeleken wordt met het starten van parenterale voeding op dag 1. Deze resultaten kwamen overeen met wat gezien werd in de gehele groep in het PEPaNIC onderzoek. Het onthouden van parenterale voeding verminderde het risico op nieuwe infecties en verhoogde de waarschijnlijkheid om

levend van de PICU en uit het ziekenhuis ontslagen te worden en ook de waarschijnlijkheid om levend van de ademhalingsondersteuning af te komen. Er was geen significant effect op de veiligheidsuitkomsten. Bovendien had de groep kinderen die geen parenterale voeding kreeg niet meer achteruitgang van hun lichaamsgewicht dan de groep kinderen die wel parenterale voeding kreeg, hoewel dit slechts in een deel van de groep onderzocht kon worden (n=100). In de subgroep van ernstig ondervoede kinderen werden dezelfde resultaten gevonden. Samengevat, er is geen ondersteunend bewijs voor het vroeg starten van parenterale voeding in kinderen die ondervoed zijn bij opname op de PICU; juist het laat starten van parenterale voeding bleek gunstig te zijn.

Hoofdstuk 5

Een van de grote zorgen die geuit werd door voedingsdeskundigen nadat de resultaten van het PEPaNIC onderzoek gepubliceerd werden, was het effect van het onthouden van parenterale voeding op het gewichtsbeloop vanwege de verminderde voedingsinname bij deze strategie. Daarom hebben we voor hoofdstuk 5 een subgroep geselecteerd met kinderen in het PEPaNIC onderzoek die gewichtsmetingen hadden bij opname en ontslag van de PICU (n=470) om het gewichtsbeloop te onderzoeken. Wij vonden dat minder verslechtering van het gewicht geassocieerd was met een lager risico op nieuwe infecties en een hogere waarschijnlijkheid om levend ontslagen te worden van de PICU. Het onthouden van parenterale voeding had geen invloed op de mate van gewichtsverslechtering. Er lijkt dus geen rol voor vroege parenterale voeding in de acute fase van ziekte te zijn om gewichtsverslechtering te voorkomen. Wat betreft korte termijn gewichtsveranderingen kan het niet geven van parenterale voeding als veilig worden beoordeeld.

Hoofdstuk 6

Zoals beschreven in hoofdstuk 1 zouden klinische uitkomsten de belangrijkste uitkomstmaten moeten zijn bij het evalueren van (voedings-)interventies. Omdat het percentage kinderen dat kritieke ziekte overleeft in gestegen naar >95%, is de lange termijn uitkomst van deze PICU-overlevenden een belangrijk aspect. Een aantal onderzoeken, gedaan in verschillende PICU populaties, hebben gevonden dat PICU overlevenden vaak geconfronteerd worden met lange termijn gevolgen, zowel in lichamelijk functioneren als ontwikkeling. Van een eerder follow-up onderzoek hebben we geleerd dat een metabole interventie tijdens PICU opname de lange termijn ontwikkeling positief kan beïnvloeden. Daarom hebben de kinderen in het PEPaNIC onderzoek 2 jaar na opname op de PICU onderzocht op onder andere lichamelijk en mentale ontwikkeling, met een parallelle groep van gezonde kinderen van dezelfde leeftijd en geslacht. Met de bekende korte termijn resultaten van het PEPaNIC onderzoek en de resultaten zoals beschreven in hoofdstukken 3 en 4 in ons achterhoofd – betere korte termijn uitkomsten met onthouden van parenterale voeding, maar een hoger risico op lage bloedsuikers – keken wij uit naar deze lange termijn resultaten.

PICU-overlevenden presteerden slechter in vele opzichten vergeleken met gezonde controle-kinderen. Bovendien vonden wij dat het niet geven van parenterale voeding

gedurende de eerste week van opname geen negatief effect had op overlevingskansen, groei, lichamelijke gezondheid en neurocognitieve ontwikkeling, maar zelfs inhibitie (de capaciteit om primaire reacties te remmen) verbeterde in vergelijking met het vroeg starten met parenterale voeding. Er werden geen verschillen geobserveerd tussen kinderen die tijdens de eerste week van PICU-opname lage bloedsuikers hadden gehad en kinderen die geen dit niet hadden gehad.

Hoofdstuk 7

Naast de korte en lange termijn klinische consequenties van het onthouden van parenterale voeding is er ook een economisch aspect. Vanwege de stijgende zorguitgaven is er een nood aan duurzame en betaalbare beslissingen in de zorg. Om deze beslissingen te kunnen maken, moeten de kosten van een behandeling afgezet worden tegen de gezondheidswinst. Wij hebben een gezondheids-economische analyse gedaan, waarbij op microniveau de directe zorgkosten berekend werden van het vroeg versus laat starten van parenterale voeding, waaruit bleek dat het laat starten van parenterale voeding gemiddeld per patiënt ongeveer 7000 euro bespaarde. Aangezien het onthouden van parenterale voeding kostenbesparend was, afgezet tegen 7.3% afname van nieuwe infecties, was deze strategie zonder twijfel kosteneffectief. Verdere analyses, zoals het berekenen van een kosten-effectiviteitsratio, waren dus overbodig. Kinderen die opgenomen waren vanwege een medische reden anders dan neurologische ziekte hadden de grootste kostenbesparing met het onthouden van parenterale voeding, gevold door kinderen die opgenomen waren na een operatie voor iets anders dan een hartafwijking. De grootste kostenbesparing werd bereikt in de categorieën opnamekosten van PICU ligdagen, medicatiekosten en kosten voor ademhalings-ondersteuning, welke tezamen verantwoordelijk waren voor 75% van de kostenbesparing. Betreffende medicatiekosten, 80% hiervan kon toegeschreven worden aan medicatie voor “bloed en bloedvormende organen” en anti-infectie medicatie. Toen we de rol van nieuwe infecties verder onderzochten, vonden wij dat het voorkómen van nieuwe infecties een belangrijke factor was in het verlagen van de kosten. Het verschil in kosten tussen kinderen met en zonder nieuwe infecties was ongeveer 70.000 euro per patiënt in de groep waar parenterale voeding vroeg werd gestart en ongeveer 58.000 euro per patiënt in de groep waar parenterale voeding onthouden werd, wat een statistische significant verschil was. Samengevat, het voorkómen van nieuwe infecties door het niet geven van parenterale voeding was de sleutel tot verlaging van de totale directe zorgkosten.

Hoofdstuk 8

Dit hoofdstuk is een reflectie op de belangrijkste bevindingen beschreven in dit proefschrift. Implicaties van ons onderzoek voor de klinische praktijk worden beschreven. Wij concluderen dat het onthouden van parenterale voeding gedurende de eerste week van kritieke ziekte in kinderen overwogen kan worden, omdat dit voordelen had op de korte termijn – ook in neonaten en ondervoede kinderen –, op de lange termijn en vanuit een gezondheids-economisch oogpunt. Gebaseerd op onze bevindingen en de huidige literatuur doen wij

aanbevelingen voor toekomstig voedingsonderzoek om de korte en lange termijn uitkomsten van kritiek zieke kinderen verder te verbeteren. Wij stellen voor dat toekomstig onderzoek zich richt op de volgende gebieden:

- de onderliggende mechanismen van het beperken van voeding gedurende de acute fase ontrafelen;
- de optimale timing en samenstelling van (parenterale) voeding uitzoeken;
- lange termijn gevolgen van kritieke ziekte in kinderen verder evalueren.

Appendices

References
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LIST OF ABBREVIATIONS

€	Euro
ANT	Amsterdam Neuropsychological Tests
ATC classification	Anatomical therapeutical chemical classification
BIA	Bio-electrical impedance
BRIEF	Behaviour Rating Inventory of Executive Function
CBCL	Child Behaviour Checklist
CI	Confidence interval
CMS	Children's Memory Scale
DBC	'Diagnosis Therapy Combination' (translation from Dutch)
DXA	Dual X-ray absorptiometry
ECMO	Extracorporeal membrane oxygenation
EN	Enteral nutrition
EPaNIC	Early versus Late Parenteral Nutrition in Critical Illness
HDL	High-density lipoproteins
HR	Hazard ratio
ICU	Intensive care unit
IQ	Intelligence quotient
IQR	Interquartile range
LDL	Low-density lipoproteins
LOS	Length of stay
NTI	Non-thyroidal illness
OR	Odds ratio
PeLOD	Paediatric Logistic Organ Dysfunction
PEPaNIC	Paediatric Early versus Late Parenteral Nutrition in Critical Illness
PICU	Paediatric intensive care unit
PIM2	Paediatric Index of Mortality 2
PN	parenteral nutrition
RCT	Randomised controlled trial
RRT	Renal replacement therapy
SD	Standard deviation
SE	Standard error
STRONGkids	Screening Tool for Risk on Nutritional Status and Growth
US$	American Dollar
VLDL	Very-low-density lipoproteins
VMI	Visual-motor integration
WAIS	Wechsler Adult Intelligence Scale
WHO	World health organisation
WISC-III-NL	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

PHD PORTFOLIO

General information	
Name PhD student:	Esther van Puffelen
Erasmus MC Department:	Intensive Care Unit and Paediatric Surgery
PhD period:	July 2014 – Dec 2018
Promotor(s):	Prof.Dr. D Tibboel, Dr. KFM Joosten
Supervisor(s):	Dr. SCAT Verbruggen
Research school:	MGC

Training program	**Year**	**Workload**
General academic skills		
Course EndNote, PubMed and other databases	2014	1.0 ECTS
BROK	2014	1.0 ECTS
Integrity in Science	2015	0.3 ECTS
CPO-course	2015	0.3 ECTS
Research skills		
Biostatistics for Clinicians (EWP22)	2015	1.4 ECTS
Research management (MolMed)	2016	1.0 ETCS
Biomedical English Writing and Communication	2016	4.0 ECTS
Biostatistical methods I: Basic principles (CCO2)	2016	5.7 ECTS
Specific skills		
Health Economics (ESP25)	2014	1.7 ECTS
LimeSurvey	2017	0.3 ECTS
(Inter)national conferences and presentations		
PPN 2nd International Paediatric Psychology Conference, Amsterdam, The Netherlands	2014	0.3 ECTS
Symposium research group Metabolism, Endocrinology and Nutrition, *invited speaker*	2015-2018	3.0 ECTS
Theme Sophia Research Day, *oral presentation*	2017	1.0 ECTS
39th ESPEN Congress, The Hague, The Netherlands, *oral presentation*	2017	1.0 ECTS
SICK symposium, *oral presentation*	2017	1.0 ECTS
51st ESPGHAN Annual Meeting, Geneva, Switzerland, *poster of distinction*	2018	1.0 ECTS
7th Congress of EAPS, Paris, France, *oral presentation*	2018	1.0 ECTS

Seminars, workshops and meetings		
Attending and presenting at Clinical & Research Meetings KJP	2014-2018	1.0 ECTS
Attending and presenting at MEV meetings	2014-2018	1.0 ECTS
Attending and presenting at Research work meetings KJP	2014-2018	2.0 ECTS
Attending and presenting at Research meetings Paediatric Surgery	2016-2018	1.0 ECTS
Attending and presenting at Research meetings PICU	2018	0.3 ECTS
Theme Sophia Research Days	2016-2018	1.0 ECTS
Tulips Young Researchers Days	2015	0.3 ECTS
Medical Business Masterclass	2018	0.5 ECTS
Teaching tasks		
Teaching activities/Didactic skills		
'Profielwerkstuk' supervision	2014	0.3 ECTS
I. van Puffelen: Onderzoek naar het stresshormoon cortisol: wat is de invloed van ernstige stress tijdens de jeugd op de ontwikkeling van een kind?		
Master Thesis Supervision 2 students	2016-2017	2.0 ECTS
S. Beker: Weight change in critically ill children receiving late versus early parenteral nutrition		
C. Verdoorn: Implementation of withholding parenteral nutrition during the first week in critically ill children.		
Other		
Winner ESPEN Research Grant	2016	
Winner SICK Jonge Onderzoekers Prijs	2017	
Sophia Researchers Association (SOV) education committee	2016-2017	

ECTS = European Credit Transfer and Accumulation System (1 ECTS represents 28 hours)

LIST OF PUBLICATIONS

1. **van Puffelen E**, Jacobs A, Verdoorn CJM, Joosten KFM, Van den Berghe G, Ista EG, Verbruggen SCAT. Worldwide Survey of De-implementation of Initiating Parenteral Nutrition Early in Paediatric Intensive Care Units. *Under review*

2. **van Puffelen E**, Hulst JM, MD, Vanhorebeek I, Dulfer K, Van den Berghe G, Joosten KFM*, Verbruggen SCAT* (*contributed equally). Effect of Late versus Early Initiation of Parenteral Nutrition on Weight Deterioration during PICU Stay: Secondary Analysis of the PEPaNIC Randomised Controlled Trial. Clin Nutr. 2019 Mar 4. pii: S0261-5614(19)30068-8. doi: 10.1016/j.clnu.2019.02.014. [Epub ahead of print] PMID: 30879734

3. Jacobs A, Derese I, Vander Perre S, **van Puffelen E**, Verstraete S, Pauwels L, Verbruggen SCAT, Wouters PJ, Langouche L, Garcia Guerra G, Joosten KFM, Vanhorebeek I*, Van den Berghe G*(*contributed equally). The non-thyroidal illness syndrome in critically ill children: prognostic value and impact of nutritional management. Thyroid. 2019 Apr;29(4):480-492. doi: 10.1089/thy.2018.0420. PMID: 30760183

4. Malarvannan G, Onghena M, Verstraete S**, van Puffelen E,** Jacobs A, Vanhorebeek I, Verbruggen SCAT, Joosten KFM, Van den Berghe G, Jorens PG, Covaci A. Phthalate and alternative plasticizers in indwelling medical devices in pediatric intensive care units. J Hazard Mater. 2019 Feb 5;363:64-72. doi: 10.1016/j.jhazmat.2018.09.087. PMID: 30308366

5. Verstraete S, Verbruggen SC, Hordijk JA, Vanhorebeek I, Dulfer K, Güiza F, **van Puffelen E,** Jacobs A, Leys S, Durt A, Van Cleemput H, Eveleens RD, Garcia Guerra G, Wouters PJ, Joosten KF, Van den Berghe G. Long-term developmental effects of withholding parenteral nutrition for 1 week in the paediatric intensive care unit: a 2-year follow-up of the PEPaNIC international, randomised, controlled trial. Lancet Respir Med. 2019 Feb;7(2):141-153. doi: 10.1016/S2213-2600(18)30334-5. PMID: 30224325

6. **van Puffelen E**, Hulst JM, Vanhorebeek I, Dulfer K, Van den Berghe G, Verbruggen SCAT, Joosten KFM. Impact of withholding parenteral nutrition in undernourished critically ill children: preplanned secondary analyses of the PEPaNIC randomized controlled trial. JAMA Network Open. 2018;1(5):e182668. doi:10.1001/jamanetworkopen.2018.2668. PMID: 30646158

7. **van Puffelen E**, Vanhorebeek I, Joosten KFM, Wouters PJ, Van den Berghe G, Verbruggen CAT. Early versus late parenteral nutrition in critically ill, term neonates: a preplanned secondary subgroup analysis of the PEPaNIC multicentre, randomised controlled trial. The Lancet Child & Adolescent Health, Volume 2, Issue 7, 505-515 doi: 10.1016/S2352-4642(18)30131-7. PMID: 30169323

8. Boeddha NP, Kerklaan D, Dunbar A, **van Puffelen E**, Nagtzaam NMA, Vanhorebeek I, Van den Berghe G, Hazelzet JA, Joosten KF, Verbruggen SC, Dik WA, Driessen GJ. HLA-DR Expression on Monocyte Subsets in Critically Ill Children. Pediatr Infect Dis J. 2018 Oct;37(10):1034-1040. doi: 10.1097/INF.0000000000001990. PMID: 29570588

9. Verstraete S, Vanhorebeek I, **van Puffelen E**, Derese I, Ingels C, Verbruggen SC, Wouters PJ, Joosten KF, Hanot J, Guerra GG, Vlasselaers D, Lin J, Van den Berghe G. Leukocyte telomere length in paediatric critical illness: effect of early parenteral nutrition. Crit Care. 2018 Feb 21;22(1):38. doi:10.1186/s13054-018-1972-6. PMID: 29463275

10. Freijer K, **van Puffelen E**, Joosten KF, Hulst JM, Koopmanschap MA. The costs of disease related malnutrition in hospitalized children. Clin Nutr ESPEN. 2018 Feb;23:228-233. doi:10.1016/j.clnesp.2017.09.009. Epub 2017 Oct 13. PMID: 29460804

11. **van Puffelen E**, Polinder S, Vanhorebeek I, Wouters PJ, Bossche N, Peers G, Verstraete S, Joosten KFM, Van den Berghe G, Verbruggen SCAT, Mesotten D. Cost-effectiveness study of early versus late parenteral nutrition in critically ill children (PEPaNIC): preplanned secondary analysis of a multicentre randomised controlled trial. Crit Care. 2018 Jan 15;22(1):4. doi: 10.1186/s13054-017-1936-2. PMID: 29335014

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doi: 10.1097/MCO.0000000000000258. PMID: 26828582

13. **van Puffelen E**, Vriesman AW, de Mol AC, Roosen YM. An acute vomiting infant with profuse diarrhoea: enterocolitis due to non-IgE-mediated cow's milk allergy. Ned Tijdschr Geneeskd. 2014;158:A7313. PMID: 25027211

ABOUT THE AUTHOR

Esther van Puffelen was born on November 22, 1986 in Delft, the Netherlands. She is the firstborn of Cock and Ineke van Puffelen, and has a younger brother, Steven. After her graduation from Het Baken Park Lyceum in Almere (Gymnasium; 2005), she attended medical school at the University of Amsterdam.

After she obtained her medical degree (2012), she worked as a resident Paediatrics (ANIOS) at the Paediatric department of Albert Schweitzer hospital in Dordrecht (2012-2013) and at both the medium care unit and neonatal intensive care unit of Erasmus-MC Sophia Children's Hospital in Rotterdam (2013-2014). In 2014, she started on the work described in this thesis at the paediatric intensive care unit under supervision of promotors prof. Dr. D Tibboel and Dr. K.F.M. Joosten and co-promotor Dr. S.C.A.T. Verbruggen. During this period, she took part in the Sophia Researchers Association (SOV) education committee. She currently works as a youth health care physician at Rivas Zorggroep.

Esther lives in Dordrecht together with Richard Schol. They have a son, Thijn*, and a 1-year old daughter, Milou. In her spare time, she likes to travel, play badminton, and have fun with Milou.

Optimal nutrition is essential for growth and development in children. Providing optimal nutrition is challenging when a child is critically ill. This thesis focuses on the short-term consequences of the timing of initiating parenteral nutrition in critically ill children, with special attention to term neonates and undernourished children, as well as to health-economic effects.

Nowadays, most critically ill children survive, which stresses the importance of examining long-term outcomes of these children. Therefore, the children's physical and neurocognitive functioning two years after critical illness was investigated additionally and compared with healthy children's functioning, and the effect of the timing of initiating parenteral nutrition hereon.

In sum, this thesis provides insights into the literal as well as figurative price to pay for paediatric critical illness, and the role of parenteral nutrition.